



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US98/09297</p> <p>(22) International Filing Date: 7 May 1998 (07.05.98)</p> <p>(30) Priority Data:  08/852,858                      7 May 1997 (07.05.97)                      US</p> <p>(71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; Of-  office of Technology Transfer, 911 Williams Pitt Union, Pitts-  burgh, PA 15260 (US).</p> <p>(72) Inventors: SEBTI, Said, M.; 8957 Magnolia Chase Circle,  Tampa, FL 33647 (US). HAMILTON, Andrew, D.; 1  White Pine Lane, Guilford, CT 06437 (US). AUGERI,  David, J.; 6846 3rd Avenue, Kenosha, WI 53143 (US).  BARR, Kenneth, J.; 4828 N. Hermitage #3A, Chicago,  IL 60640-4143 (US). DONNER, Bernard, G.; 1901  McRae Lane, Mundelein, IL 60060 (US). FAKHOURY,  Stephen, A.; 517 Buckingham, Mundelein, IL 60060 (US).  JANOWICK, David, A.; 37070 Ganster Road, Beach  Park, IL 60087 (US). KALVIN, Douglas, M.; 1201  Lockwood Drive, Buffalo Grove, IL 60089 (US). LARSEN,</p>		<p>John, J.; 10542 Altegld Street, Melrose Park, IL 60164 (US). LIU, Gang; 838 Alderly Lane, Gurnee, IL 60031 (US). O'CONNOR, Stephen, J.; 2103 Washington Avenue, Wilmette, IL 60091 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). SHEN, Wang; 6215 Formoor Lane, Gurnee, IL 60031 (US). SWENSON, Rolf, E.; 285 Penny Lane, Grayslake, IL 60030 (US). SORENSEN, Bryan, K.; 2620 North Lewis Avenue, Waukegan, IL 60087 (US). SULLIVAN, Gerard, M.; 2214 North Sunrise Drive, Round Lake Beach, IL 60073 (US). SZCZEPANKIEWICZ, Bruce, G.; 33720 Royal Oake Lane, Apt. 209, Gages Lake, IL 60030 (US). TASKER, Andrew, S.; 6251 Eagle Ridge Drive, Gurnee, IL 60031 (US). WASICK, James, T.; 28440 Dorie Lane, Waterford, WI 53185 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, IL 60015 (US).</p> <p>(74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby &amp; Cushman, Intellectual Property Group of Pillsbury Madison &amp; Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US).</p> <p>(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b>  <i>With international search report.</i>  <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES</p>		
<div style="text-align: center;"> </div>		
<p>(57) Abstract</p> <p>Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R<sub>1</sub> is (a) hydrogen, (b) loweralkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl-L<sub>2</sub>-, and (i) heterocyclic-L<sub>2</sub>-; R<sub>2</sub> is selected from (a) (Ia), (b) -C(O)NH-CH(R<sub>14</sub>)-C(O)OR<sub>15</sub>, (c) (Ib), (d) -C(O)NH-CH(R<sub>14</sub>)-C(O)NH<sub>2</sub>SO<sub>2</sub>R<sub>16</sub>, (e) -C(O)NH-CH(R<sub>14</sub>)-tetrazolyl, (f) -C(O)NH-heterocyclic, and (g) -C(O)NH-CH(R<sub>14</sub>)-C(O)NR<sub>17</sub>R<sub>18</sub>; R<sub>3</sub> is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, (Ic), and -P(W)R<sup>R3</sup>R<sup>R3'</sup>; R<sub>4</sub> is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L<sub>1</sub> is absent or is selected from (a) -L<sub>4</sub>-N(R<sub>5</sub>)-L<sub>5</sub>-, (b) -L<sub>4</sub>-O-L<sub>5</sub>-, (c) -L<sub>4</sub>-S(O)<sub>n</sub>-L<sub>5</sub>-, (d) -L<sub>4</sub>-L<sub>6</sub>-C(W)-N(R<sub>5</sub>)-L<sub>5</sub>-, (e) -L<sub>4</sub>-L<sub>6</sub>-S(O)<sub>m</sub>-N(R<sub>5</sub>)-L<sub>5</sub>-, (f) -L<sub>4</sub>-N(R<sub>5</sub>)-C(W)-L<sub>7</sub>-L<sub>5</sub>-, (g) -L<sub>4</sub>-N(R<sub>5</sub>)-S(O)<sub>p</sub>-L<sub>7</sub>-L<sub>5</sub>-, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) (Id), and (m) (Ie) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.</p>		

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## INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

Technical Field

10           The present invention relates to novel compounds which are useful in inhibiting protein isoprenyl transferases (for example, protein farnesyltransferase and protein geranylgeranyltransferase) and the farnesylation or geranylgeranylation of the oncogene protein Ras and other related small g-proteins, compositions containing such compounds and methods of using such compounds.

Background of the Invention

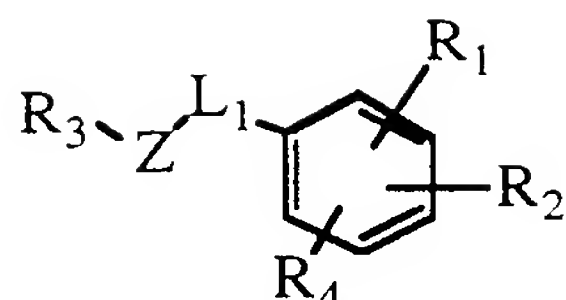
15           Ras oncogenes are the most frequently identified activated oncogenes in human tumors. Transformed protein Ras is involved in the proliferation of cancer cells. The Ras must be farnesylated before this proliferation can occur. Farnesylation of Ras by farnesyl pyrophosphate (FPP) is effected by protein farnesyltransferase. Inhibition of protein farnesyltransferase, and thereby farnesylation of the Ras protein, blocks the ability of transformed cells to proliferate. Inhibition of protein geranylgeranyltransferase and, thereby, of geranylgeranylation of Ras proteins, also results in down regulation of Ras protein function.

20           Activation of Ras and other related small g-proteins that are farnesylated and/or geranylated also partially mediates smooth muscle cell proliferation (Circulation, I-3: 88 (1993), which is hereby incorporated herein by reference). Inhibition of protein isoprenyl transferases, and thereby farnesylation or geranylgeranylation of the Ras protein, also aids in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis, a condition which compromises the success of angioplasty and surgical bypass for obstructive vascular lesions.

25           There is therefore a need for compounds which are inhibitors of protein farnesyltransferase and protein geranylgeranyltransferase.

Summary of the Invention

30           In its principle embodiment, the invention provides a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, wherein

40

$R_1$  is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- 45 (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl- $L_2$ - wherein aryl is selected from the group consisting of
- 50 (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- 55 (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

or Z wherein X, Y, and Z are independently selected from the

group consisting of

- alkenyl,
- 60 alkynyl,
- alkoxy,
- aryl,
- carboxy,
- cyano,
- 65 halogen,
- haloalkyl,
- hydroxy,
- hydroxyalkyl,
- loweralkyl,
- 70 nitro,

N-protected amino, and

-NRR' wherein R and R' are independently selected

from the group consisting of

hydrogen and

75 loweralkyl,

oxo (=O), and

thioalkoxy and

L<sub>2</sub> is absent or is selected from the group consisting of

-CH<sub>2</sub>-,

80 -CH<sub>2</sub>CH<sub>2</sub>-,

-CH(CH<sub>3</sub>)-,

-O-,

-C(O)-,

-S(O)<sub>q</sub> wherein q is 0, 1 or 2, and

85 -N(R)-, and

(10) heterocycle-L<sub>2</sub>- wherein L<sub>2</sub> is as defined above and the heterocycle is

unsubstituted or substituted with 1, 2, 3 or 4 substituents

independently selected from the group consisting of

(a) loweralkyl,

90 (b) hydroxy,

(c) hydroxyalkyl,

(d) halogen

(e) cyano,

(f) nitro,

95 (g) oxo (=O),

(h) -NRR',

(i) N-protected amino,

(j) alkoxy,

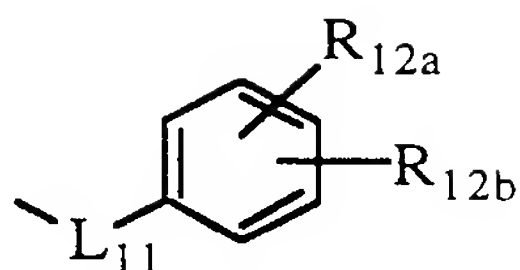
(k) thioalkoxy,

100 (l) haloalkyl,

(m) carboxy, and

(n) aryl;

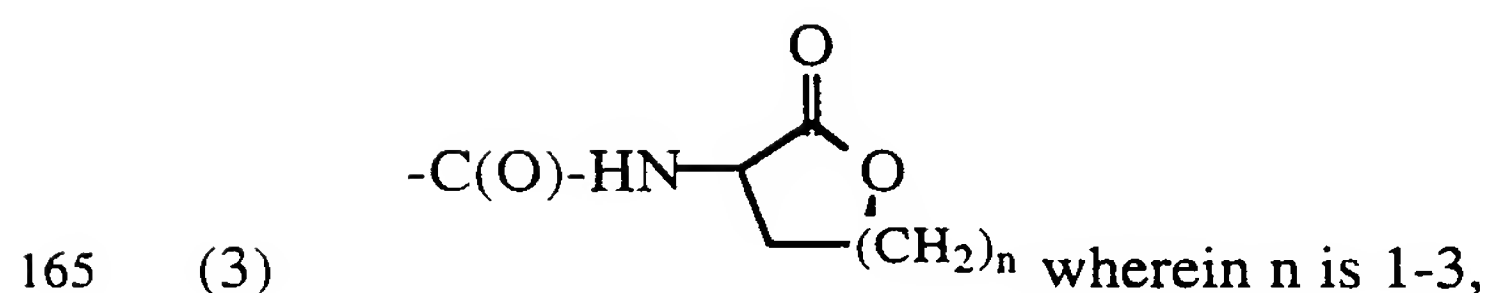
**R<sub>2</sub>** is selected from the group consisting of



- 105 (1) wherein  $L_{11}$  is selected from the group  
 consisting of  
 (a) a covalent bond,  
 (b)  $-C(W)N(R)-$  wherein  $R$  is defined previously and  $W$  is  
 selected from the group consisting of  $O$  and  $S$ ,  
 110 (c)  $-C(O)-$ ,  
 (d)  $-N(R)C(W)-$ ,  
 (e)  $-CH_2O-$ ,  
 (f)  $-C(O)O-$ , and  
 (g)  $-CH_2N(R)-$ ,  
 115  $R_{12a}$  is selected from the group consisting of  
 (a) hydrogen,  
 (b) loweralkyl, and  
 (c)  $-C(O)OR_{13}$  wherein  $R_{13}$  is selected from the group  
 consisting of  
 120 hydrogen and  
 a carboxy-protecting group, and  
 $R_{12b}$  is selected from the group consisting of  
 (a) hydrogen and  
 (b) loweralkyl,  
 125 with the proviso that  $R_{12a}$  and  $R_{12b}$  are not both hydrogen,

- (2)  $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$  wherein  $L_{11}$  is defined previously,  
 $R_v$  is selected from the group consisting of  
 (a) hydrogen and  
 130 (b) loweralkyl,  
 $R_{15}$  is selected from the group consisting of  
 (a) hydrogen,  
 (b) alkanoyloxyalkyl,  
 (c) loweralkyl, and  
 135 (b) a carboxy-protecting group, and  
 $R_{14}$  is selected from the group consisting of  
 (a) alkoxyalkyl,  
 (b) alkoxyarylalkyl,

- 140 (c) alkoxycarbonylalkyl,  
 (d) alkylsulfinylalkyl,  
 (e) alkylsulfonylalkyl,  
 (f) alkynyl,  
 (g) aminoalkyl,  
 (h) aminocarbonylalkyl,  
 145 (i) aminothiocabonylalkyl,  
 (j) aryl,  
 (k) arylalkyl,  
 (l) carboxyalkyl,  
 (m) cyanoalkyl,  
 150 (n) cycloalkyl,  
 (o) cycloalkylalkoxyalkyl,  
 (p) cycloalkylalkyl,  
 (q) (heterocyclic)alkyl,  
 (r) hydroxyalkyl,  
 155 (s) hydroxyarylalkyl,  
 (t) loweralkyl,  
 (u) sulfhydrylalkyl,  
 (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is  
 unsubstituted or substituted with 1, 2, 3, or 4  
 160 substituents selected from the group consisting of  
 halogen,  
 (w) thioalkoxyalkylamino, and  
 (x) thiocycloalkyloxyalkyl,



- (4)  $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(\text{O})\text{NH}\text{SO}_2\text{R}_{16}$  wherein  $\text{R}_{14}$  is defined previously  
 and  $\text{R}_{16}$  is selected from the group consisting of  
 170 (a) loweralkyl,  
 (b) haloalkyl,  
 (c) aryl wherein the aryl is unsubstituted or substituted with  
 1, 2, 3, 4, or 5 substituents independently  
 selected from the group consisting of



- 175 loweralkyl,  
hydroxy,  
hydroxyalkyl,  
halogen,  
cyano,  
nitro,  
180 oxo (=O),  
-NRR'  
N-protected amino,  
alkoxy,  
thioalkoxy,  
185 haloalkyl,  
carboxy, and  
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or  
substituted with substituents independently  
190 selected from the group consisting of  
loweralkyl,  
hydroxy,  
hydroxyalkyl,  
halogen,  
195 cyano,  
nitro,  
oxo (=O),  
-NRR',  
N-protected amino,  
200 alkoxy,  
thioalkoxy,  
haloalkyl,  
carboxy, and  
aryl;
- 205
- (5) -C(O)NH-CH(R<sub>14</sub>)-tetrazolyl wherein the tetrazole ring is unsubstituted  
or substituted with loweralkyl or haloalkyl,
- (6) -L<sub>11</sub>-heterocycle,
- 210

- (7)  $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(\text{O})\text{NR}_{17}\text{R}_{18}$  wherein  $\text{R}_{14}$  is defined previously  
and  $\text{R}_{17}$  and  $\text{R}_{18}$  are independently selected from the group  
consisting of

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

215

- 220 (8)  $-\text{C}(\text{O})\text{OR}_{15}$ , and

- (9)  $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})$ -heterocycle wherein  $\text{R}_{14}$  is as previously defined  
and the heterocycle is unsubstituted or substituted with  
loweralkyl or haloalkyl;

225

$\text{L}_1$  is absent or is selected from the group consisting of

- (1)  $-\text{L}_4-\text{N}(\text{R}_5)-\text{L}_5-$  wherein  $\text{L}_4$  is absent or selected from the group  
consisting of

- (a)  $\text{C}_1$ -to- $\text{C}_{10}$ -alkylene and
- (b)  $\text{C}_2$ -to- $\text{C}_{16}$ -alkenylene,

230

wherein the alkylene and alkenylene groups are unsubstituted or  
substituted with 1, 2, 3 or 4 substituents independently  
selected from the group consisting of

alkenyl,

235

alkenyloxy,

alkenyloxyalkyl,

alkenyl $[\text{S}(\text{O})_q]$ alkyl,

alkoxy,

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or

240

substituted with 1 or 2 hydroxyl substituents,

with the proviso that no two hydroxyls are attached to the  
same carbon,

alkoxycarbonyl wherein the alkoxycarbonyl is

unsubstituted or substituted with 1, 2, or 3

245

substituents independently selected from the

group consisting of

halogen and

250                   cycloalkyl,  
                  alkylsilyloxy,  
                  alkyl[S(O)<sub>q</sub>],  
                  alkyl[S(O)<sub>q</sub>]alkyl,  
                  aryl wherein the aryl is unsubstituted or substituted with  
                  1, 2, 3, 4, or 5 substituents independently  
                  selected from the group consisting of  
255                   alkoxy wherein the alkoxy is unsubstituted or  
                  substituted with substituents selected  
                  from the group consisting of cycloalkyl,  
                  aryl,  
                  arylalkyl,  
260                   aryloxy wherein the aryloxy is unsubstituted or  
                  substituted with 1, 2, 3, 4, or 5  
                  substituents independently selected from  
                  the group consisting of,  
                  halogen,  
265                   nitro, and  
                  -NRR',  
                  cycloalkyl,  
                  halogen,  
                  loweralkyl,  
270                   hydroxyl,  
                  nitro,  
                  -NRR', and  
                  -SO<sub>2</sub>NRR',  
                  arylalkoxy wherein the arylalkoxy is unsubstituted or  
275                   substituted with substituents selected from the  
                  group consisting of alkoxy,  
                  arylalkyl,  
                  arylalkyl[S(O)<sub>q</sub>]alkyl,  
                  aryl[S(O)<sub>q</sub>],  
280                   aryl[S(O)<sub>q</sub>]alkyl wherein the aryl[S(O)<sub>q</sub>]alkyl is  
                  unsubstituted or substituted with 1, 2, 3, 4, or 5  
                  substituents independently selected from  
                  alkoxy and  
                  loweralkyl,

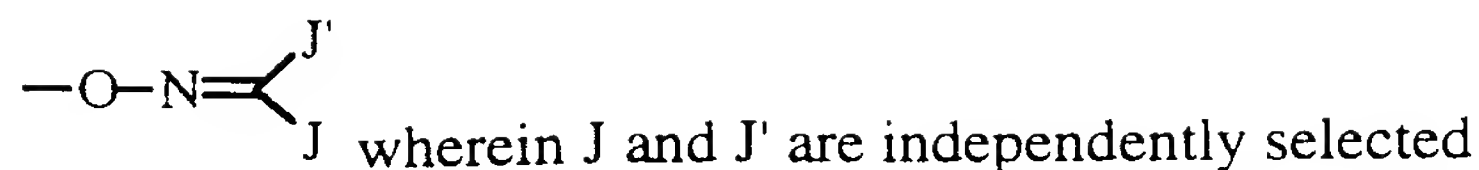
285 arylalkoxyalkyl wherein the arylalkoxyalkyl is  
unsubstituted or substituted with substituents  
selected from the group consisting of  
alkoxy, and  
halogen,  
290 aryloxy,  
aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or  
substituted with substituents selected from the  
group consisting of halogen,  
carboxyl,  
295  $-C(O)NR_C R_D$  wherein  $R_C$  and  $R_D$  are independently  
selected from the group consisting of  
hydrogen,  
loweralkyl, and  
alkoxycarbonyl or  
300  $R_C$  and  $R_D$  together with the nitrogen to which  
they are attached form a ring selected  
from the group consisting of  
morpholine,  
piperidine,  
305 pyrrolidine  
thiomorpholine,  
thiomorpholine sulfone, and  
thiomorpholine sulfoxide,  
wherein the ring formed by  $R_C$  and  $R_D$   
310 together is unsubstituted or  
substituted with 1 or 2  
substituents independently  
selected from the group consisting  
of alkoxy and alkoxyalkyl,  
315 cycloalkenyl wherein the cycloalkenyl is unsubstituted or  
substituted with 1 or 2 substituents selected from  
the group consisting of alkenyl,  
cycloalkoxy,  
cycloalkoxycarbonyl,  
320 cycloalkoxyalkyl,  
cycloalkyl wherein the cycloalkyl is unsubstituted or

substituted with 1, 2, 3, 4, or 5 substituents  
independently selected from the group consisting  
of aryl,  
325 loweralkyl, and  
alkanoyl,  
cycloalkylalkoxy,  
cycloalkylalkoxycarbonyl,  
cycloalkylalkoxyalkyl,  
330 cycloalkylalkyl,  
cycloalkyl[S(O)<sub>q</sub>]alkyl,  
cycloalkylalkyl[S(O)<sub>q</sub>]alkyl,  
fluorenyl,  
heterocycle wherein the heterocycle is unsubstituted or  
335 substituted with 1, 2, 3, or 4 substituents  
independently selected from the group  
consisting of  
alkoxy wherein the alkoxy is unsubstituted or  
substituted with 1 or 2 substituents  
340 independently selected from the group  
consisting of aryl and cycloalkyl,  
alkoxyalkyl wherein the alkoxyalkyl is  
unsubstituted or substituted with 1 or 2  
substituents independently selected from  
345 the group consisting of  
aryl and  
cycloalkyl,  
alkoxycarbonyl wherein the alkoxycarbonyl is  
unsubstituted or substituted with 1 or 2  
350 substituents independently selected from  
the group consisting of  
aryl and  
cycloalkyl,  
aryl wherein the aryl is unsubstituted or  
355 substituted with 1, 2, 3, 4, or 5  
substituents independently selected from  
the group consisting of  
alkanoyl,



360                   alkoxy,  
                      carboxaldehyde,  
                      haloalkyl,  
                      halogen,  
                      loweralkyl,  
                      nitro,  
365                   -NRR', and  
                      thioalkoxy,  
  
                      arylalkyl,  
                      aryloxy,  
                      cycloalkoxyalkyl,  
370                   cycloalkyl,  
                      cycloalkylalkyl,  
                      halogen,  
                      heterocycle,  
                      hydroxyl,  
375                   loweralkyl wherein the loweralkyl is  
                              unsubstituted or substituted with 1, 2, or  
                              3 substituents independently selected  
                              from the group consisting of  
                              heterocycle,  
380                   hydroxyl,  
                      with the proviso that no two hydroxyls  
                              are attached to the same carbon,  
                              and  
                      -NR<sup>R3</sup>R<sup>R3'</sup> wherein R<sup>R3</sup> and R<sup>R3'</sup> are  
385                   independently selected from the  
                              group consisting of  
                              hydrogen  
                              aryl,  
                              loweralkyl,  
390                   aryl,  
                              arylalkyl,  
                              heterocycle,  
                              (heterocyclic)alkyl,  
                              cycloalkyl, and  
395                   cycloalkylalkyl, and

sulfhydryl,  
(heterocyclic)alkoxy,  
(heterocyclic)alkyl,  
(heterocyclic)alkyl[S(O)<sub>q</sub>]alkyl,  
400 (heterocyclic)oxy,  
(heterocyclic)alkoxyalkyl,  
(heterocyclic)oxyalkyl,  
heterocycle[S(O)<sub>q</sub>]alkyl,  
hydroxyl,  
405 hydroxyalkyl,  
imino,  
N-protected amino,  
=N-O-aryl, and  
=N-OH,  
410 =N-O-heterocycle wherein the heterocycle is  
unsubstituted or substituted with 1, 2, 3, or 4  
substituents independently selected from the  
group consisting of  
loweralkyl,  
415 hydroxy,  
hydroxyalkyl,  
halogen,  
cyano,  
nitro,  
420 oxo (=O),  
-NRR'  
N-protected amino,  
alkoxy,  
thioalkoxy,  
425 haloalkyl,  
carboxy, and  
aryl,  
=N-O-loweralkyl,  
-NRR<sup>3</sup>R<sup>3'</sup>,  
430 -NHNR<sub>C</sub>R<sub>D</sub>,  
-OG wherein G is a hydroxyl protecting group,  
-O-NH-R,



from the group consisting of

435

loweralkyl and  
arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

440

oxyaminocarbonylalkyl,

-SO<sub>2</sub>-A wherein A is selected from the group

consisting of

loweralkyl,

aryl, and

445

heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

450

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

455

sulfhydryl,

thioxo, and

thioalkoxy,

L<sub>5</sub> is absent or selected from the group consisting of

(a) C<sub>1</sub>-to-C<sub>10</sub>-alkylene and

460

(b) C<sub>2</sub>-to-C<sub>16</sub>-alkenylene

wherein (a) and (b) are unsubstituted or substituted as

defined previously, and

R<sub>5</sub> is selected from the group consisting of

hydrogen,

465

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

group consisting of aryl,

alkoxy,  
alkoxyalkyl,  
470 alkoxycarbonyl wherein the alkoxycarbonyl is  
unsubstituted or substituted with 1, 2 or 3  
substituents independently selected from the  
group consisting of  
aryl and  
475 halogen,  
alkylaminocarbonylalkyl wherein the  
alkylaminocarbonylalkyl is unsubstituted or  
substituted with 1 or 2 substituents  
independently selected from the group consisting  
480 of aryl,  
(anthracenyl)alkyl,  
aryl,  
arylalkoxy,  
arylalkyl wherein the arylalkyl is unsubstituted or  
485 substituted with 1, 2, 3, 4, or 5 substituents  
independently selected from the group  
consisting of  
alkoxy,  
aryl,  
490 carboxyl,  
cyano,  
halogen,  
haloalkoxy,  
haloalkyl,  
495 nitro,  
oxo, and  
-L<sub>11</sub>-C(R<sub>14</sub>)(R<sub>v</sub>)-C(O)OR<sub>15</sub>,  
(aryl)oyl wherein the (aryl)oyl is unsubstituted or  
substituted with substituents selected from the  
500 group consisting of halogen,  
aryloxycarbonyl,  
carboxaldehyde,  
-C(O)NRR',  
cycloalkoxycarbonyl,

505 cycloalkylaminocarbonyl,  
 cycloalkylaminothiocarbonyl,  
 cyanoalkyl,  
 cyclolalkyl,  
 cycloalkylalkyl wherein the cycloalkylalkyl is  
 510 unsubstituted or substituted with 1 or 2 hydroxyl  
 substituents,  
 with the proviso that no two hydroxyls are attached to the  
 same carbon,  
 (cyclolalkyl)oyl,  
 515 (9,10-dihydroanthracenyl)alkyl wherein the  
 (9,10-dihydroanthracenyl)alkyl is unsubstituted  
 or substituted with 1 or 2 oxo substituents,  
 haloalkyl,  
 heterocycle,  
 520 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is  
 unsubstituted or substituted with 1, 2, 3, 4, or 5  
 substituents selected from the group consisting of  
 loweralkyl,  
 (heterocyclic)oyl,  
 525 loweralkyl, wherein the loweralkyl is unsubstituted  
 or substituted with substituents selected from the  
 group consisting of -NRR',  
 -SO<sub>2</sub>-A, and  
 thioalkoxyalkyl;

530

(3) -L<sub>4</sub>-S(O)<sub>m</sub>-L<sub>5</sub>- wherein L<sub>4</sub> and L<sub>5</sub> are defined previously and m is 0, 1,  
 or 2,

535 (4) -L<sub>4</sub>-L<sub>6</sub>-C(W)-N(R<sub>6</sub>)-L<sub>5</sub>- wherein L<sub>4</sub>, W, and L<sub>5</sub> are defined previously,  
 R<sub>6</sub> is selected from the group consisting of  
 (a) hydrogen,  
 (b) loweralkyl,  
 (c) aryl,  
 540 (d) arylalkyl,  
 (e) heterocycle,



- (f) (heterocyclic)alkyl,  
 (g) cyclolakyl, and  
 (h) cycloalkylalkyl, and  
 545  $L_6$  is absent or is selected from the group consisting of  
 (a) -O-,  
 (b) -S-, and  
 (c) -N(R<sub>6</sub>)- wherein R<sub>6</sub> is selected from the group  
 consisting of  
 550 hydrogen,  
 loweralkyl,  
 aryl,  
 arylalkyl,  
 heterocycle,  
 555 (heterocyclic)alkyl,  
 cyclolakyl, and  
 cycloalkylalkyl,
- (5) -L<sub>4</sub>-L<sub>6</sub>-S(O)<sub>m</sub>-N(R<sub>5</sub>)-L<sub>5</sub>-,  
 560  
 (6) -L<sub>4</sub>-L<sub>6</sub>-N(R<sub>5</sub>)-S(O)<sub>m</sub>-L<sub>5</sub>-,  
 (7) -L<sub>4</sub>-N(R<sub>5</sub>)-C(W)-L<sub>7</sub>-L<sub>5</sub>- wherein L<sub>4</sub>, R<sub>5</sub>, W, and L<sub>5</sub> are  
 defined previously and L<sub>7</sub> is absent or is selected from the group  
 565 consisting of -O- and -S-,
- (8) C<sub>1</sub>-C<sub>10</sub>-alkylene wherein the alkylene group is unsubstituted or  
 substituted with 1 or 2 substituents independently selected from  
 the group consisting of  
 570 (a) aryl,  
 (b) arylalkyl,  
 (c) heterocycle,  
 (d) (heterocyclic)alkyl,  
 (e) cyclolakyl,  
 575 (f) cycloalkylalkyl,  
 (g) alkylthioalkyl, and  
 (h) hydroxy,

(9) C<sub>2</sub>-to-C<sub>10</sub>-alkenylene wherein the alkenylene group is unsubstituted or  
 580 substituted with 1 or 2 substituents independently selected from  
 the group consisting of

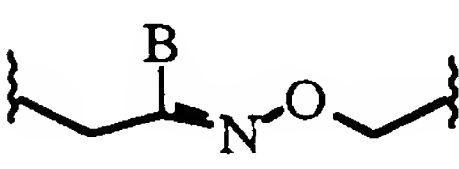
- (a) aryl,
- (b) arylalkyl,
- (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is  
 585 unsubstituted or substituted with 1, 2, 3, 4, or 5  
 substituents selected from the group consisting  
 of halogen,
- (d) heterocycle,
- (e) (heterocycle)alkyl,
- 590 (f) hydroxyalkyl,
- (g) cyclolalkyl,
- (h) cycloalkylalkyl,
- (i) alkylthioalkyl, and
- (j) hydroxy,

595 (10) C<sub>2</sub>-to-C<sub>10</sub>-alkynylene wherein the alkynylene group is unsubstituted or  
 substituted with 1 or 2 substituents independently selected from  
 the group consisting of

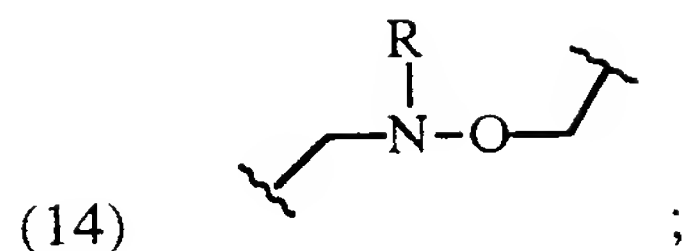
- (a) aryl,
- 600 (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolalkyl,
- (f) cycloalkylalkyl,
- 605 (g) alkylthioalkyl, and
- (h) hydroxy,

(11) -L<sub>4</sub>-heterocycle-L<sub>5</sub>-,

610 (12) a covalent bond,

(13)  wherein B is selected from the group consisting of  
 loweralkyl and  
 arylalkyl, and

615



**Z** is selected from the group consisting of

- (1) a covalent bond,
- 620 (2) -O-,
- (3) -S(O)<sub>q</sub>-, and
- (4) -NR<sub>Z</sub>- wherein R<sub>Z</sub> is selected from the group consisting of
  - (a) hydrogen
  - (b) loweralkyl,
  - 625 (c) aryl,
  - (d) arylalkyl,
  - (e) heterocycle,
  - (f) (heterocyclic)alkyl,
  - (g) cyclolalkyl, and
  - 630 (h) cycloalkylalkyl;

**R<sub>3</sub>** is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- 635 (3) fluorenyl,
- (4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

- (a) alkanoyl,
- 640 (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
  - halogen,
  - aryl, and
  - 645 cycloalkyl,
- (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents independently selected from the group consisting of aryl and

- 650 cycloalkyl,
- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of aryl, and
- 655 cycloalkyl,
- (e) alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the
- 660 group consisting of alkanoyl, alkoxy wherein the alkoxy is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of cycloalkyl,
- 665 carboxaldehyde, haloalkyl, halogen, loweralkyl, nitro,
- 670 -NRR', and thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of,
- 675 halogen, nitro, and -NRR',
- (j) (aryl)oyl,
- 680 (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR'' wherein R is defined previously and R'' is selected from the group consisting of
- 685 hydrogen, loweralkyl, and

- carboxyalkyl,
- (o) cyano,
- (p) cyanoalkyl,
- 690 (q) cycloalkyl,
- (r) cycloalkylalkyl,
- (s) cycloalkoxyalkyl,
- (t) halogen,
- (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
- 695 with 1, 2, 3, 4, or 5 hydroxyl substituents,  
with the proviso that no two hydroxyls are attached to the same  
carbon,
- (v) heterocycle,
- (w) hydroxyl,
- 700 (x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or  
substituted with substituents selected from the group  
consisting of aryl,
- (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
- 705 with substituents selected from the group consisting of  
heterocycle,  
hydroxyl,  
with the proviso that no two hydroxyls are attached to the  
same carbon,
- NR<sup>3</sup>R<sup>3'</sup>, and
- 710 -P(O)(OR)(OR'),
- (z) nitro,
- (aa) -NRR',
- (bb) oxo,
- (cc) -SO<sub>2</sub>NR<sub>A</sub>'R<sub>B</sub>' wherein R<sub>A</sub>' and R<sub>B</sub>' are independently selected
- 715 from the group consisting of  
hydrogen,  
(aryl)oyl,  
loweralkyl, and  
heterocycle wherein the heterocycle is unsubstituted or
- 720 substituted with 1, 2, or 3 substituents  
independently selected from the group consisting  
of loweralkyl,
- (dd) sulfhydryl, and



(ee) thioalkoxy,

725

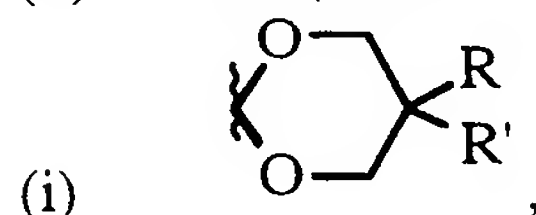
- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from the group consisting of

730

- (a) alkoxy,
- (b) aryl,
- (c) arylalkoxy
- (d) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

735

- (e) loweralkyl,
- (f) halogen,
- (g)  $\text{NR}^3\text{R}^{3'}$ ,
- (h) oxo, and



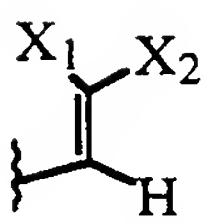
740

- (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

745

- (a) loweralkyl,
- (b) alkoxy,
- (c) halogen,
- (d) aryl,
- (e) aryloxy,
- (f) alkanoyl, and
- (g)  $\text{NR}^3\text{R}^{3'}$ ,

750

- (7)  wherein  $\text{X}_1$  and  $\text{X}_2$  together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

755

- (8)  $-\text{P}(\text{W})\text{R}^3\text{R}^{3'}$ ; and

$\text{R}_4$  is selected from the group consisting of

- (1) hydrogen,  
 (2) loweralkyl,  
 760 (3) haloalkyl  
 (4) halogen,  
 (5) aryl,  
 (6) arylalkyl,  
 (7) heterocycle,  
 765 (8) (heterocyclic)alkyl  
 (9) alkoxy, and  
 (10) -NRR'; or

**L<sub>1</sub>, Z, and R<sub>3</sub>** together are selected from the group consisting of

- 770 (1) aminoalkyl,  
 (1) haloalkyl,  
 (2) halogen,  
 (3) carboxaldehyde, and  
 (4) (carboxaldehyde)alkyl, and  
 775 (5) hydroxyalkyl,

with the proviso that when **L<sub>1</sub>, Z, and R<sub>3</sub>** together are (1)-(5), **R<sub>1</sub>** is other than hydrogen.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with a pharmaceutically acceptable carrier.

780 In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting protein isoprenyl transferases (i.e., protein farnesyltransferase and/or  
 785 geranylgeranyltransferase) in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound of formula I.

In yet another aspect of the present invention is disclosed a method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase or both.

790 In yet another aspect of the present invention is disclosed a method for treatment of conditions mediated by farnesylated or geranylgeranylated proteins, for example, treatment of Ras associated tumors in humans and other mammals.

In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal comprising administering to the patient a

795 therapeutically effective amount of a compound of the invention alone or in combination  
with another chemotherapeutic agent

In yet another aspect of the present invention is disclosed a method for treating or  
preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal  
comprising administering to the mammal a therapeutically effective amount of a compound  
800 of claim 1.

The compounds of the invention can comprise asymmetrically substituted carbon  
atoms. As a result, all stereoisomers of the compounds of the invention are meant to be  
included in the invention, including racemic mixtures, mixtures of diastereomers, as well as  
single diastereomers of the compounds of the invention. The terms "S" and "R"  
805 configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for  
Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30, which is  
hereby incorporated herein by reference.

#### Detailed Description

810

#### Definitions of Terms

As used herein the terms "Cys," "Glu," "Leu," "Lys," "Met," "nor-Leu,"  
"nor-Val," "Phe," "Ser" and "Val" refer to cysteine, glutamine, leucine, lysine, methionine,  
norleucine, norvaline, phenylalanine, serine and valine in their L-, D- or DL forms. As  
used herein these amino acids are in their naturally occurring L- form.

815

As used herein, the term "carboxy protecting group" refers to a carboxylic acid  
protecting ester group employed to block or protect the carboxylic acid functionality while  
the reactions involving other functional sites of the compound are carried out. Carboxy  
protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp.  
152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy  
820 protecting group can be used as a prodrug whereby the carboxy protecting group can be  
readily cleaved *in vivo* (for example by enzymatic hydrolysis) to release the biologically  
active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug  
concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium  
Series, American Chemical Society (1975), which is hereby incorporated herein by  
825 reference. Such carboxy protecting groups are well known to those skilled in the art,  
having been extensively used in the protection of carboxyl groups in the penicillin and  
cephalosporin fields (as described in U.S. Pat. No. 3,840,556 and 3,719,667, the  
disclosures of which are hereby incorporated herein by reference). Examples of esters  
useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21  
830 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche,  
Pergamon Press, New York (1987), which is hereby incorporated herein by reference.

Representative carboxy protecting groups are C<sub>1</sub> to C<sub>8</sub> loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or cycloalkyloxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; aryloxycarbonyloxyalkyl, such as 2-(phenoxycarbonyloxy)ethyl, 2-(5-indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and the like; arylalkyloxycarbonyloxyalkyl, such as 2-(benzyloxycarbonyloxy)ethyl and the like; arylalkenyloxycarbonyloxyalkyl, such as 2-(3-phenylpropen-2-yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated herein by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, a,a-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to  $R_{29}C(O)-$  wherein  $R_{29}$  is a loweralkyl group. The alkanoyl groups of this invention can be optionally substituted.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{71}-NH-$  wherein  $R_{71}$  is an alkanoyl group. The alkanoylaminoalkyl groups of this invention can be optionally substituted.

The term "alkanoyloxy" as used herein refers to  $R_{29}C(O)-O-$  wherein  $R_{29}$  is a loweralkyl group. The alkanoyloxy groups of this invention can be optionally substituted.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group. The alkanoyloxyalkyl groups of this invention can be optionally substituted.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenyl include  $-CH=CH_2$ ,  $-CH_2CH=CH_2$ ,  $-C(CH_3)=CH_2$ ,



905 -CH<sub>2</sub>CH=CHCH<sub>3</sub>, and the like. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 20 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include  
910 -CH=CH-, -CH<sub>2</sub>CH=CH-, -C(CH<sub>3</sub>)=CH-, -CH<sub>2</sub>CH=CHCH<sub>2</sub>-, and the like. The alkenylene groups of this invention can be optionally substituted.

The term "alkenyloxy" as used herein refers to an alkenyl group attached to the parent molecular group through an oxygen atom. The alkenyloxy groups of this invention can be optionally substituted.

915 The term "alkenyloxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkenyloxy group. The alkenyloxyalkyl groups of this invention can be optionally substituted.

The term "alkoxy" as used herein refers to R<sub>30</sub>O- wherein R<sub>30</sub> is loweralkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like. The alkoxy groups of this invention can be optionally substituted.  
920

The term "alkoxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkoxy" as used herein refers to R<sub>31</sub>O-R<sub>32</sub>O- wherein R<sub>31</sub> is loweralkyl as defined above and R<sub>32</sub> is an alkylene radical. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like. The alkoxyalkoxy groups of this invention can be optionally substituted.  
925

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl  
930 include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R<sub>66</sub>-C(O)-O- wherein R<sub>66</sub> is an alkoxyalkyl group.

The term "alkoxyarylalkyl" as used herein refers to an arylalkyl group to which is  
935 attached an alkoxy group. The alkoxyarylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the  
940 like. The alkoxycarbonyl groups of this invention can be optionally substituted. The alkoxycarbonyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylalkyl" as used herein refers to an alkoxycarbonyl group as previously defined appended to a loweralkyl radical. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like. The  
945 alkoxycarbonylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{69}\text{-NH-}$  wherein  $R_{69}$  is an alkoxycarbonyl group. The alkoxycarbonylaminoalkyl groups of this invention can be optionally substituted.

950 The term "alkoxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{63}\text{-O-}$  wherein  $R_{63}$  is an alkoxycarbonyl group. The alkoxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "alkylamino" as used herein refers to  $R_{35}\text{NH-}$  wherein  $R_{35}$  is a loweralkyl group, for example, methylamino, ethylamino, butylamino, and the like. The alkylamino groups of this invention can be optionally substituted.

955 The term "alkylaminoalkyl" as used herein refers a loweralkyl radical to which is appended an alkylamino group. The alkylaminoalkyl groups of this invention can be optionally substituted.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{70}\text{-C(O)-NH-}$  wherein  $R_{70}$  is an alkylamino group. The  
960 alkylaminocarbonylaminoalkyl groups of this invention can be optionally substituted.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be  
965 optionally substituted.

The term "alkylsilyloxy" as used herein refers to a loweralkyl group to which is attached  $\text{-OSiR}_W\text{R}_X\text{R}_Y$  wherein  $R_W$ ,  $R_X$ , and  $R_Y$  are selected from the group consisting of loweralkyl.

970 The term "alkylsulfinyl" as used herein refers to  $R_{33}\text{S(O)-}$  wherein  $R_{33}$  is a loweralkyl group. The alkylsulfinyl groups of this invention can be optionally substituted.

The term "alkylsulfinylalkyl" as used herein refers to an alkyl group to which is attached a alkylsulfinyl group. The alkylsulfinylalkyl groups of this invention can be optionally substituted.

975 The term "alkylsulfonyl" as used herein refers to  $R_{34}\text{S(O)}_2\text{-}$  wherein  $R_{34}$  is a loweralkyl group. The alkylsulfonyl groups of this invention can be optionally substituted.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylsulfonyl group. The alkylsulfonylalkyl groups of this invention can be optionally substituted.

980 The term alkylthioalkyl as used herein refers to a lower alkyl group as defined herein attached to the parent molecular moiety through a sulfur atom and an alkylene group. The alkylthioalkyl groups of this invention can be optionally substituted.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include  $-C\equiv CH$ ,  $-CH_2C\equiv CH$ ,  $-CH_2C\equiv CCH_3$ , and the like.  
985 The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynylene include  $-C\equiv C-$ ,  $-CH_2C\equiv C-$ ,  $-CH_2C\equiv CCH_2-$ , and the like. The alkynylene groups of this invention can be  
990 optionally substituted.

The term "amino" as used herein refers to  $-NH_2$ .

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group. The aminocarbonyl groups of this invention can be optionally substituted.

995 The term "aminocarbonylalkyl" as used herein refers to an alkyl group to which is attached an aminocarbonyl group. The aminocarbonylalkyl groups of this invention can be optionally substituted.

The term "aminoalkyl" as used herein refers to a loweralkyl radical to which is appended an amino group. The aminoalkyl groups of this invention can be optionally  
1000 substituted.

The term "aminothiocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a thiocarbonylcarbonyl ( $C=S$ ) group. The aminothiocarbonyl groups of this invention can be optionally substituted.

1005 The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aryloxy group (i.e.,  $R_{61}-C(O)O-$  wherein  $R_{61}$  is an aryl group). The aryloxyalkyl groups of this invention can be optionally substituted.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl  
1010 groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, sulfhydryl, nitro, cyano, carboxaldehyde, carboxy, alkoxycarbonyl, haloalkyl- $C(O)-NH-$ , haloalkenyl- $C(O)-NH-$  and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.



1015 The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group. The arylalkenyl groups of this invention can be optionally substituted.

The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{68}-O-C(O)-O-$  wherein  $R_{68}$  is an arylalkenyl group. The arylalkenyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1020 The term "arylalkoxy" as used herein refers to an alkoxy group to which is attached an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like. The arylalkyl groups of this invention can be optionally substituted.

1025 The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e.,  $R_{62}C(O)O-$  wherein  $R_{62}$  is an arylalkyl group). The arylalkylcarbonyloxyalkyl groups of this invention can be optionally substituted.

1030 The term "aryloxy" as used herein refers to an aryl group attached to the parent molecular group through an oxygen atom. The aryloxy groups of this invention can be optionally substituted.

The term "aryloxycarbonyl" as used herein refers to an aryloxy group attached to the parent molecular group through a carbonyl group. The aryloxycarbonyl groups of this invention can be optionally substituted.

1035 The term "aryloyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The aryloyl groups of this invention can be optionally substituted.

1040 The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{67}-O-C(O)-O-$  wherein  $R_{67}$  is an arylalkyl group. The arylalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{65}-O-$  wherein  $R_{65}$  is an aryl group. The aryloxyalkyl groups of this invention can be optionally substituted.

1045 The term "arylalkoxy" as used herein refers to an alkoxy radical to which is appended  $R_{65}-O-$  wherein  $R_{65}$  is an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

1050 The term "arylalkyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group. The arylalkyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to  $R_{65}\text{-O-}$  wherein  $R_{65}$  is an aryl group. The aryloxy groups of this invention can be optionally substituted. The aryloxy groups of this invention can be optionally substituted.

1055 The term "(aryl)oyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The (aryl)oyl groups of this invention can be optionally substituted.

1060 The term "aryloxythioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{75}\text{-S-}$  wherein  $R_{75}$  is an aryloxyalkyl group. The aryloxythioalkoxyalkyl groups of this invention can be optionally substituted.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{65}\text{-O-C(O)-O-}$  wherein  $R_{65}$  is an aryl group. The aryloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1065 The term "arylsulfonyl" as used herein refers to  $R_{36}\text{S(O)}_2\text{-}$  wherein  $R_{36}$  is an aryl group. The arylsulfonyl groups of this invention can be optionally substituted.

The term "arylsulfonyloxy" as used herein refers to  $R_{37}\text{S(O)}_2\text{O-}$  wherein  $R_{37}$  is an aryl group. The arylsulfonyloxy groups of this invention can be optionally substituted.

The term "carboxy" as used herein refers to  $\text{-COOH}$ .

1070 The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy ( $\text{-COOH}$ ) group. The carboxyalkyl groups of this invention can be optionally substituted.

The term "cyanoalkyl" as used herein used herein refers to a loweralkyl radical to which is appended a cyano ( $\text{-CN}$ ) group. The cyanoalkyl groups of this invention can be optionally substituted.

1075 The term "carboxaldehyde" as used herein used herein refers to  $\text{-CHO}$ .

The term "(carboxaldehyde)alkyl" as used herein used herein refers to a carboxaldehyde group attached to a loweralkyl group. The (carboxaldehyde)alkyl groups of this invention can be optionally substituted.

1080 The terms "cycloalkanoyl" and "(cycloalkyl)oyl" refer to a cycloalkyl group attached to the parent molecular group through a carbonyl group. The cycloalkanoyl and (cycloalkyl)oyl groups of this invention can be optionally substituted.

The term "cycloalkanoylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyl group (i.e.,  $R_{60}\text{-C(O)-}$  wherein  $R_{60}$  is a cycloalkyl group). The cycloalkanoylalkyl groups of this invention can be optionally substituted.

1085 The term "cycloalkylalkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a cycloalkyl group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1090 The term "cycloalkenyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms and containing a carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like. The cycloalkenyl groups of this invention can be optionally substituted.

The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through an oxygen atom. The cycloalkoxy groups of this invention can be optionally substituted.

1095 The term "cycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a cycloalkoxy group. The cycloalkoxyalkyl groups of this invention can be optionally substituted.

1100 The term "cycloalkoxycarbonyl" as used herein refers to a cycloalkoxy group attached to the parent molecular group through a carbonyl group. The cycloalkoxycarbonyl groups of this invention can be optionally substituted.

1105 The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. The cycloalkyl groups of this invention can be optionally substituted. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylaminocarbonyl" as used herein refers to  $\text{NHR}_{60}\text{C}(\text{O})-$  wherein  $\text{R}_{60}$  is a cycloalkyl group. The cycloalkylaminocarbonyl groups of this invention can be optionally substituted.

1110 The term "cycloalkylaminothiocarbonyl" as used herein refers to  $\text{NHR}_{60}\text{C}(\text{S})-$  wherein  $\text{R}_{60}$  is defined above. The cycloalkylaminothiocarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxy" as used herein refers to an alkoxy radical to which is appended a cycloalkyl group. The cycloalkylalkoxy groups of this invention can be optionally substituted.

1115 The term "cycloalkylalkoxyalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkylalkoxy group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1120 The term "cycloalkylalkoxycarbonyl" as used herein refers to a cycloalkylalkoxy radical attached to the parent molecular group through a carbonyl group. The cycloalkylalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like. The cycloalkylalkyl groups of this invention can be optionally substituted.

1125 The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{64}-O-C(\ddot{O})-O-$  wherein  $R_{64}$  is a cycloalkyl group. The cycloalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "dialkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two alkoxy groups. The dialkoxyalkyl groups of this invention can be optionally substituted.

1130 The term "dialkylamino" as used herein refers to  $R_{38}R_{39}N-$  wherein  $R_{38}$  and  $R_{39}$  are independently selected from loweralkyl, for example dimethylamino, diethylamino, methylpropylamino, and the like. The dialkylamino groups of this invention can be optionally substituted.

1135 The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group. The dialkylaminoalkyl groups of this invention can be optionally substituted.

The term "dialkylaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{73}-C(O)-$  wherein  $R_{73}$  is a dialkylamino group. The dialkylaminocarbonylalkyl groups of this invention can be optionally substituted.

1140 The term "dioxoalkyl" as used herein refers to a loweralkyl radical which is substituted with two oxo ( $=O$ ) groups. The dioxoalkyl groups of this invention can be optionally substituted.

The term "dithioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two thioalkoxy groups. The dithioalkoxyalkyl groups of this invention can be optionally substituted.

The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

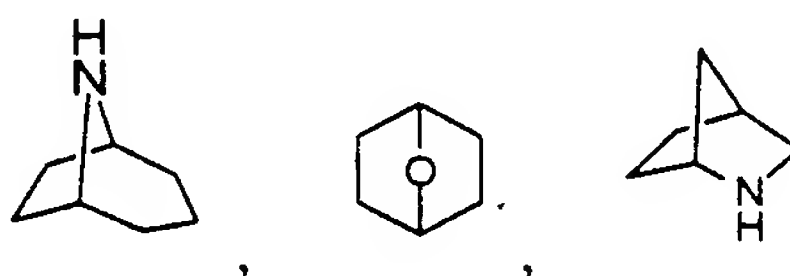
1150 The term "haloalkenyl" as used herein refers to an alkenyl radical, as defined above, bearing at least one halogen substituent. The haloalkenyl groups of this invention can be optionally substituted.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorides.

1155 The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent

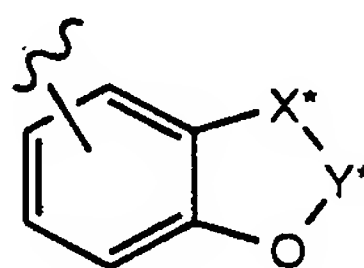


positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2  
 1165 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The term "heterocyclic" also includes bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from the group consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring and another monocyclic heterocyclic ring (for example, indolyl, quinolyl,  
 1170 isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl,  
 1175 indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuranyl and benzothienyl. Heterocyclics also include bridged bicyclic groups wherein  
 1180 a monocyclic heterocyclic group is bridged by an alkylene group, for example,



and the like.

Heterocyclics also include compounds of the formula



1185 wherein X\* is -CH<sub>2</sub>-, -CH<sub>2</sub>O- or -O- and Y\* is -C(O)- or -(C(R''))<sub>v</sub> - wherein R'' is hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

Heterocyclics can be unsubstituted or substituted with one, two, three, four or five  
 1190 substituents independently selected from the group consisting of  
 a) hydroxy, b) -SH, c) halo, d) oxo (=O), e) thioxo (=S), f) amino, g) -NHOH, h) alkylamino, i) dialkylamino, j) alkoxy, k) alkoxyalkoxy, l) haloalkyl, m) hydroxyalkyl, n) alkoxyalkyl, o) cycloalkyl which is unsubstituted or substituted with one, two, three or four

- loweralkyl groups, p) cycloalkenyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, q) alkenyl, r) alkynyl, s) aryl, t) arylalkyl, u) -COOH, v) -SO<sub>3</sub>H, w) loweralkyl, x) alkoxycarbonyl, y) -C(O)NH<sub>2</sub>, z) -C(S)NH<sub>2</sub>, aa) -C(=N-OH)NH<sub>2</sub>, bb) aryl-L<sub>16</sub>-C(O)- wherein L<sub>16</sub> is an alkenylene radical, cc) -S-L<sub>17</sub>-C(O)OR<sub>40</sub> wherein L<sub>17</sub> is an alkylene radical which is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR<sub>41</sub>R<sub>42</sub> wherein R<sub>41</sub> is hydrogen or loweralkyl and R<sub>42</sub> is loweralkyl) and R<sub>40</sub> is hydrogen or a carboxy-protecting group, dd) -S-L<sub>18</sub>-C(O)NR<sub>43</sub>R<sub>44</sub> wherein L<sub>18</sub> is an alkylene radical which is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR<sub>41</sub>R<sub>42</sub> wherein R<sub>41</sub> is hydrogen or loweralkyl and R<sub>43</sub> and R<sub>44</sub> are independently selected from the group consisting of hydrogen, loweralkyl and aryl, ee) -S-L<sub>19</sub>-CN wherein L<sub>19</sub> is an alkylene radical, ff) -S-L<sub>20</sub>-R<sub>45</sub> wherein L<sub>20</sub> is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with oxo (=O) and R<sub>45</sub> is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, gg) -O-L<sub>21</sub>-R<sub>46</sub> wherein L<sub>21</sub> is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR<sub>41</sub>R<sub>42</sub> wherein R<sub>41</sub> is hydrogen or loweralkyl and R<sub>46</sub> is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, hh) -O-S(O)<sub>2</sub>-R<sub>47</sub> wherein R<sub>47</sub> is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ii) -S(O)<sub>2</sub>-NH-R<sub>48</sub> wherein R<sub>48</sub> is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, jj) alkylsulfinyl, kk) alkylsulfonyl, ll) arylsulfonyl, mm) arylsulfonyloxy, nn) -C(=NOR<sub>49</sub>)C(O)OR<sub>50</sub> wherein R<sub>49</sub> is hydrogen or loweralkyl and R<sub>50</sub> is hydrogen or a carboxy-protecting group, oo) alkoxycarbonylalkyl,

pp) carboxyalkyl, qq) cyanoalkyl, rr) alkylaminoalkyl, ss) N-protected alkylaminoalkyl, tt) dialkylaminoalkyl, uu) dioxoalkyl, vv) loweralkyl-C(O)-, ww) loweralkyl-C(S)-, xx) aryl-C(O)-, yy) aryl-C(S)-, zz) loweralkyl-C(O)-O-, aaa) loweralkyl-S-C(S)- bbb) N-protected amino, ccc) aminoalkyl-C(O)-, ddd) N-protected aminoalkyl-C(O)- eee) aminoalkyl-C(S)-, 1235 fff) N-protected aminoalkyl-C(S)-, ggg) aminoalkyl, hhh) N-protected aminoalkyl, iii) formyl, jjj) cyano, kkk) nitro, lll) spiroalkyl, mmm) oxoalkyloxy, nnn)  $R_{53}$ - $L_{22}$ -, wherein  $L_{22}$  is alkenylene or alkynylene and  $R_{53}$  is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, 1240 N-protected amino, alkoxy, thioalkoxy and haloalkyl, ooo) aryl-NH-C(O)-, ppp)  $R_{54}$ -N=N- wherein  $R_{54}$  is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, qqq) =N- $R_{55}$  wherein  $R_{55}$  is hydrogen, 1245 aryl, heterocyclic, -S(O)<sub>2</sub>-aryl or -S(O)<sub>2</sub>-heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, rrr) diarylalkyl-N=N-, sss) aryl-N( $R_{56}$ )- or arylalkyl-N( $R_{56}$ )- wherein  $R_{56}$  is hydrogen or an N-protecting group, ttt) aryl- 1250 sulfonylalkyl, uuu) heterocyclicsulfonylalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, vvv) =C(CN)(C(O)NH<sub>2</sub>), www) =C(CN)(C(O)O-loweralkyl), xxx) heterocyclic or heterocyclicalkyl wherein the heterocyclic 1255 is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, yyy) hydroxythioalkoxy, zzz) aryloxyalkyl, aaaa) aryloxyalkylthioalkoxy, bbbb) dialkoxyalkyl, cccc) dithioalkoxyalkyl, dddd) arylalkyl-NH- $L_{23}$ - wherein  $L_{23}$  is an alkylene group, eeee) heterocyclicalkyl-NH- 1260  $L_{24}$ - wherein  $L_{24}$  is an alkylene group, ffff) aryl-S(O)<sub>2</sub>-NH- $L_{25}$ - wherein  $L_{25}$  is an alkylene group, gggg) heterocyclic-S(O)<sub>2</sub>-NH- $L_{26}$ - wherein  $L_{26}$  is an alkylene group, hhhh) aryl-C(O)-NH- $L_{27}$ - wherein  $L_{27}$  is an alkylene group and iiiii) heterocyclic-C(O)-NH- $L_{28}$ - wherein  $L_{28}$  is an alkylene group, jjjj)  $R_{yy}(\text{CH}_2)_n\text{-X-Y-Z-(CH}_2)_m$  wherein  $R_{yy}$  is cycloalkyl, aryl and loweralkyl, n and m are independently 0-2, Z is O or absent, Y is 1265 absent, CH<sub>2</sub>, CHOH or C(O), with the proviso that when X is O, Z is absent and with the proviso that when Z is O, X is absent and with the proviso that when Y is CHOH, X and Z are absent.

The term "(heterocyclic)alkoxy" as used herein refers to an alkoxy group to which is attached a heterocycle. The (heterocyclic)alkoxy groups of this invention can be optionally substituted.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like. The (heterocyclic)alkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)oxy" as used herein refers to a heterocycle connected to the parent molecular group through an oxygen atom. The (heterocyclic)oxy groups of this invention can be optionally substituted.

The term "(heterocyclic)oxyalkyl" as used herein refers to a loweralkyl group to which is attached a (heterocyclic)oxy group. The (heterocyclic)oxyalkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)alkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a heterocycle. The (heterocyclic)alkoxyalkyl groups of this invention can be optionally substituted.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended  $R_{72}-C(O)-O-$  wherein  $R_{72}$  is a heterocyclic group. The heterocycliccarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein refers to  $-OH$ .

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended an hydroxy group. The hydroxyalkyl groups of this invention can be optionally substituted.

The term "hydroxyarylalkyl" as used herein refers to a arylalkyl group to which is appended a hydroxy group. The hydroxyarylalkyl groups of this invention can be optionally substituted.

The term "hydroxythioalkoxy" as used herein refers to  $R_{51}S-$  wherein  $R_{51}$  is a hydroxyalkyl group. The hydroxythioalkoxy groups of this invention can be optionally substituted.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like. The loweralkyl groups of this invention can be optionally substituted.

The term "N-protected alkylaminoalkyl" as used herein refers to an alkylaminoalkyl group wherein the nitrogen is N-protected. The N-protected alkylaminoalkyl groups of this invention can be optionally substituted.

The term "nitro" as used herein refers to  $-NO_2$ .



1305 The term "oxo" as used herein refers to (=O).

The term "oxoalkyloxy" as used herein refers to an alkoxy radical wherein the loweralkyl moiety is substituted with an oxo (=O) group. The oxoalkyloxy groups of this invention can be optionally substituted.

1310 The term "oxyamino(alkyl)carbonylalkyl" as used herein refers to a -O-NR-C(O)-R' group wherein R and R' are loweralkyl.

The term "oxyamino(arylalkyl)carbonylalkyl" as used herein refers to a -O-NR<sup>R3</sup>-C(O)-R group wherein R<sup>R3</sup> is arylalkyl and R is loweralkyl.

The term "oxyaminocarbonylalkyl" as used herein refers to -O-NH-C(O)-R group wherein R is loweralkyl.

1315 The term "spiroalkyl" as used herein refers to an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfhydryl" as used herein refers to -SH.

1320 The term "sulfhydrylalkyl" as used herein refers to a loweralkyl group to which is attached a sulfhydryl group. The sulfhydrylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy" as used herein refers to R<sub>52</sub>S- wherein R<sub>52</sub> is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like. The thioalkoxy groups of this invention can be optionally substituted.

1325 The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl group as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like. The thioalkoxyalkyl groups of this invention can be optionally substituted.

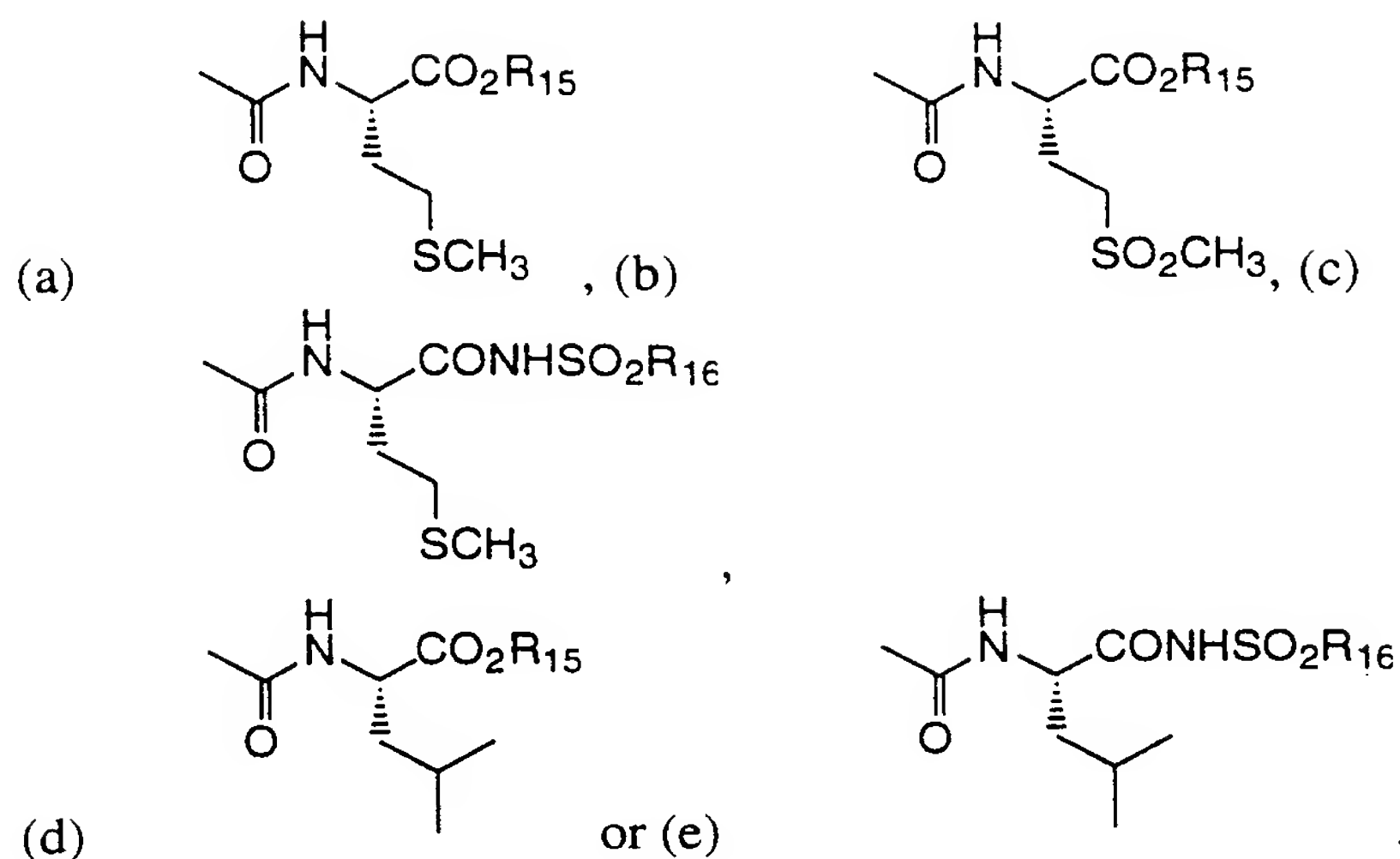
1330 The term "thiocycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through a sulfur atom. The thiocycloalkoxy groups of this invention can be optionally substituted.

The term "thiocycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a thiocycloalkoxy group. The thiocycloalkoxyalkyl groups of this invention can be optionally substituted.

1335 Preferred embodiments

Preferred compounds of the invention are compounds of formula I wherein R<sub>1</sub> is unsubstituted or substituted phenyl and R<sub>2</sub> is -C(O)NH-CH(R<sub>14</sub>)-C(O)OR<sub>15</sub> or -C(O)NH-CH(R<sub>14</sub>)-C(O)NHSO<sub>2</sub>R<sub>16</sub> wherein R<sub>14</sub>, R<sub>15</sub> and R<sub>16</sub> are defined above.

1340 More preferred compounds of the invention are compounds of formula I wherein R<sub>1</sub> is unsubstituted or substituted phenyl and R<sub>2</sub> is

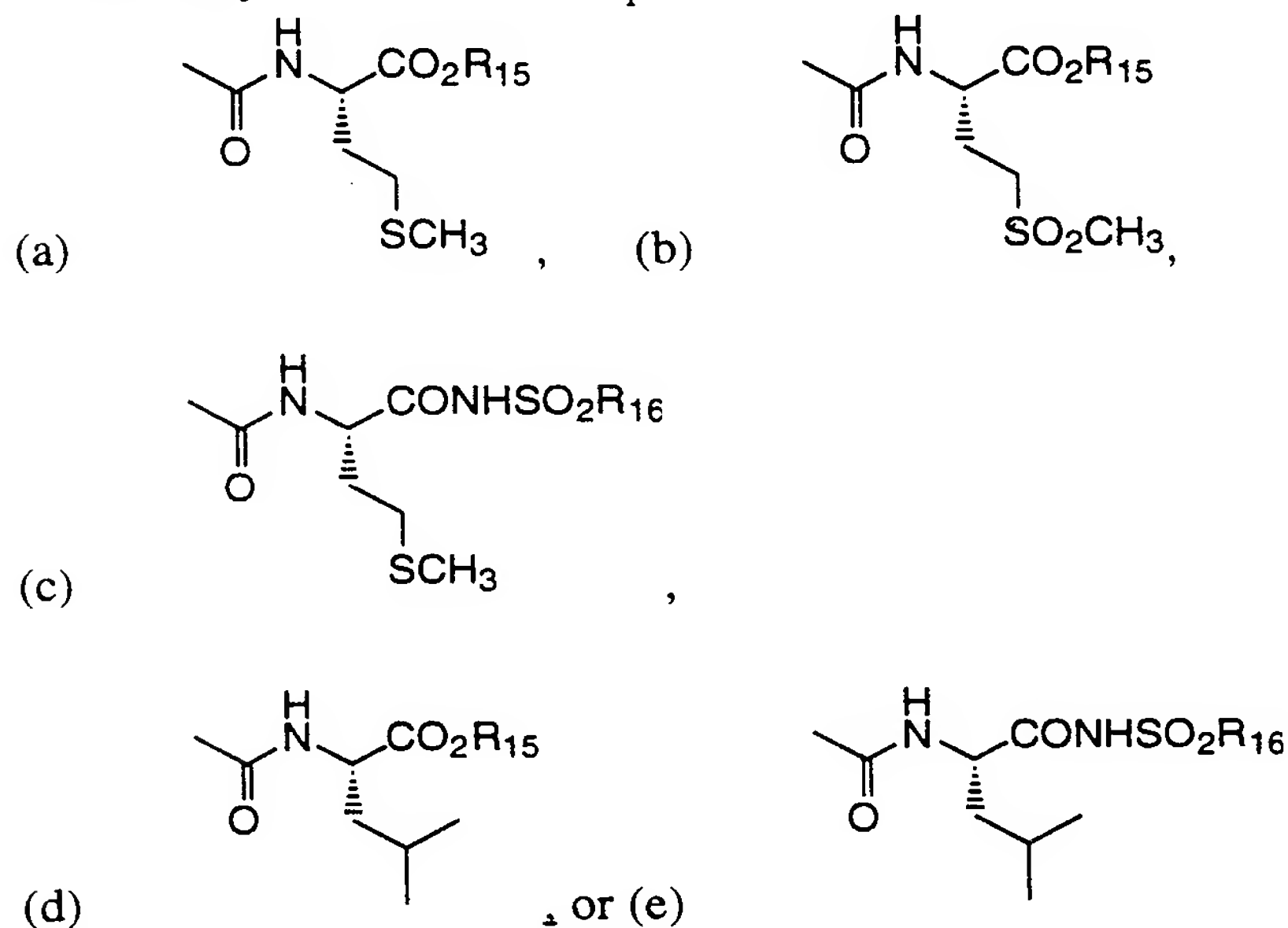


1345

Still more preferred compounds have formula I wherein  $R_3$  is selected from the group consisting of (a) pyridyl, (b) imidazolyl, and (c) furyl wherein the pyridyl, imidazolyl, or furyl group may be substituted with 1, 2 or 3 substituents selected from the group consisting of aryl, loweralkyl, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, amino, N-protected amino, alkoxy, and thioalkoxy.

1350

Still more preferred compounds of the invention have the structure defined immediately above wherein  $R_1$  is unsubstituted or substituted phenyl and  $R_2$  is



1355

The most preferred compounds have the structure defined immediately above wherein  $R_3$  is unsubstituted or substituted pyridyl or imidazolyl.

1360

Protein Farnesyltransferase Inhibition

The ability of the compounds of the invention to inhibit protein farnesyltransferase or protein geranylgeranyltransferase can be measured according to the method of Moores, et al., J. Biol. Chem. 266: 14603 (1991) or the method of Vogt, et al., J. Biol. Chem. 270:660-664 (1995). In addition, procedures for determination of the inhibition of farnesylation of the oncogene protein Ras are described by Goldstein, et al., J. Biol. Chem., 266:15575-15578 (1991) and by Singh in United States Patent No. 5,245,061.

In addition, *in vitro* inhibition of protein farnesyltransferase may be measured by the following procedure. Rat brain protein farnesyltransferase activity is measured using an Amersham Life Science commercial scintillation proximity assay kit and substituting a biotin-K Ras B fragment (biotin-Lys-Lys-Ser-Lys-Thr-Lys-Cys-Val-Ile-Met-CO<sub>2</sub>H), 0.1 mM final concentration, for the biotin-lamin substrate provided by Amersham. The enzyme is purified according to Reiss, Y., et al., Cell, 62: 81-88 (1990), utilizing steps one through three. The specific activity of the enzyme is approximately 10 nmol substrate farnesylated/mg enzyme/hour. The percent inhibition of the farnesylation caused by the compounds of the invention (at  $10 \times 10^{-6}$  M) compared to an uninhibited control sample is evaluated in the same Amersham test system.

The % inhibition of protein farnesyltransferase was determined for representative compounds of the invention. The results are summarized in Table 1.

## Tables 1-5

*In Vitro* Potencies of Representative Compounds

Table 1. Inhibition of farnesyltransferase

1385

Example	% inhibition at 1X10 <sup>-5</sup> M	Example	% inhibition at 1X10 <sup>-5</sup> M
200	93	674	40
350	53	676	76
351	82	678	73
352	52	680	58
353	62	683	57
354	47	684	48
355	43	685	55
356	58	686	48
357	56	687	78
358	45	688	71
359	36	689	73
360	88	690	61
361	97	692	74
362	83	699	74
363	96	700	68
364	69	701	64
365	97	702	79
366	83	704	67
367	81	705	72
368	71	706	53
369	87	707	66
370	86	708	76
371	66	709	55
372	69	710	45
373	76	711	46
374	61	712	69
375	68	713	40
376	80	714	56
377	71	715	67
378	54	717	75

380	45	718	40
381	79	750	44
382	> 50	752	58
383	> 50	753	55
387	> 50	754	40
388	> 50	755	44
390	> 50	756	47
639	44	757	58
659	55	758	46
663	43	759	49
664	75	952	> 50
669	52	955	50
670	78	974	> 50
672	48		

Table 2. Inhibition of farnesyltransferase

Example	% inhibition at $1 \times 10^{-6}$ M	Example	% inhibition at $1 \times 10^{-6}$ M
157	92	583	98
158	2	587	97
159	84	595	97
160	30	607	96
161	54	610	94
162	12	613	97
163	18	617	99
164	92	620	98
165	74	626	61
166	97	627	85
167	98	632	43
168	92	633	32
183	98	636	72
184	36	641	34
185	93	642	48
186	86	644	54
187	68	386	> 50
188	40	399	> 50
189	88	403	99
190	4	404	98
191	28	405	98
192	95	406	95
193	4	407	98
196	43	435	96
197	1	451	85
201	63	452	96
202	31	453	90
203	76	456	81
204	98	457	92
205	98	460	88
206	67	463	91
207	98	465	92
208	98	466	93

209	74	467	97
210	5	468	96
211	98	469	92
212	12	470	95
213	98	471	94
214	97	472	97
215	82	473	96
216	67	474	92
217	99	475	21
218	89	476	91
219	56	477	98
220	92	478	98
221	55	479	95
222	41	480	87
223	63	481	95
224	41	488	41
225	93	494	96
226	23	495	95
227	94	496	93
228	39	497	94
231	50	498	98
233	65	499	98
234	4	500	98
235	95	501	84
237	98	502	24
238	22	503	57
239	97	504	90
240	98	505	72
241	41	507	95
242	99	507	96
243	23	508	95
244	21	509	77
245	50	510	84
248	79	512	94
249	77	513	96
250	96	514	94

252	98	515	72
253	99	516	95
254	96	525	99
255	98	528	99
256	98	529	99
257	98	530	94
258	98	537	97
259	98	540	40
260	98	645	37
261	98	646	58
262	98	649	86
263	99	650	68
264	98	651	33
265	98	652	41
266	97	653	62
267	96	655	35
268	98	657	32
269	98	658	73
270	98	661	45
271	84	662	68
272	96	665	55
273	96	666	82
274	94	667	83
276	98	671	36
277	98	673	59
278	99	677	37
279	99	682	31
280	98	691	34
281	98	693	53
282	76	694	45
283	98	696	57
284	83	697	39
286	84	703	40
287	24	716	69
288	22	719	90
289	23	720	70



290	74	721	83
291	23	722	96
292	36	723	87
294	98	724	87
295	94	725	78
296	89	726	81
297	65	727	95
298	43	744	84
299	94	749	84
300	22	751	32
301	98	764	88
302	31	765	76
304	99	768	67
305	99	771	72
306	99	772	79
307	82	773	41
308	62	774	48
309	98	775	32
310	98	776	36
311	97	777	83
313	94	782	96
314	97	786	34
315	93	787	70
316	63	788	44
317	54	789	86
318	98	790	88
319	98	791	53
320	93	792	88
321	90	793	94
322	98	794	92
323	98	796	35
324	98	797	35
325	99	806	72
326	91	807	90
327	97	808	88
328	96	809	78

329	98	810	89
330	98	812	94
331	98	813	95
332	26	816	87
333	99	824	90
334	93	831	92
343	72	832	80
344	95	834	55
345	91	835	96
346	98	844	92
347	95	846	85
348	66	850	90
349	99	862	95
379	21	866	62
541	37	867	71
542	67	868	89
544	35	872	74
545	88	878	95
546	97	879	95
547	91	886	35
550	96	889	95
	78	902	85
728			
552	88	903	78
553	92	908	88
554	96	910	42
555	85	911	65
556	99	918	97
557	93	923	78
560	91	924	77
561	91	925	87
564	98	926	69
565	94	936	
			69
566	98	937	95
568	93	962	> 50

569	91	964	> 50
572	91	979	26
575	70	982	64
576	88	987	93
577	94	988	92
582	99	989	88

1390 Table 3. Inhibition of farnesyltransferase

Example	% inhibition at $1 \times 10^{-7}$ M	Example	% inhibition at $1 \times 10^{-7}$ M
434	93	623	96
436	89	729	73
437	89	730	96
438	90	731	65
439	80	732	84
440	92	733	60
441	91	734	49
442	88	735	96
443	97	736	96
444	95	737	95
445	94	738	54
446	91	739	83
447	91	740	94
448	92	741	89
449	91	742	87
450	96	743	51
455	83	745	93
458	87	746	84
459	92	747	68
461	93	748	56
462	91	769	90
464	86	770	91
482	96	781	91
483	95	785	96
484	97	795	87
485	96	798	95
486	97	799	96
487	81	800	74
489	86	801	87
490	70	802	88
491	94	811	85
492	95	814	81
493	51	815	71

511	82	817	60
519	89	818	78
520	97	822	93
521	94	823	75
522	93	825	79
523	97	839	63
524	99	849	66
526	96	854	78
527	97	855	92
531	74	856	97
532	88	857	92
533	91	859	86
534	84	861	65
535	89	863	72
536	79	864	84
539	89	865	95
548	86	869	92
549	98	874	90
551	93	875	92
558	87	876	92
559	96	891	94
562	95	893	87
563	95	894	89
570	92	895	92
571	88	896	96
573	72	900	95
574	81	906	88
578	90	912	85
579	92	913	89
580	90	914	91
581	96	917	78
584	96	919	91
585	96	921	82
589	91	929	81
590	95	931	98
592	93	933	91

593	86	935	72
594	95	940	92
597	75	941	90
600	93	945	80
601	92	947	79
602	97	948	75
604	86	949	57
609	95	950	71
611	95	951	71
615	94	959	> 50
616	95	983	66
618	89	984	86
621	98	990	84
622	95	993	90

Table 4. Inhibition of farnesyltransferase

Example	% inhibition at $1 \times 10^{-8}$ M	Example	% inhibition at $1 \times 10^{-8}$ M
384	91	851	82
397	50	852	79
398	> 50	853	85
400	98	858	60
401	66	860	85
408	> 95	870	91
409	84	871	94
410	94	873	97
517	92	877	68
518	90	880	95
567	69	881	69
586	90	882	79
588	68	883	91
591	82	884	94
599	86	885	95
603	94	887	92
605	68	888	86
606	93	892	59
608	91	897	76
612	96	898	82
614	92	899	88
619	95	901	84
760	95	904	85
762	84	905	86
763	92	907	79
766	95	909	79
767	97	916	96
779	70	920	96
780	71	922	96
803	95	927	74
804	95	928	84
805	96	930	66
819	76	932	60

820	66	934	71
821	75	938	61
826	92	939	72
827	77	942	58
828	87	943	79
829	92	944	88
833	78	946	52
836	95	954	> 50
837	91	958	> 50
838	92	960	> 50
840	73	985	89
841	93	986	95
842	88	991	69
843	96	992	93
845	85	994	83
847	85	995	92
848	87	996	80



Table 5. Inhibition of geranylgeranyltransferase I.

Example	Activity
387	> 50% inhibition at $1 \times 10^{-6}$ M
388	> 50% inhibition at $1 \times 10^{-7}$ M
389	> 50% inhibition at $1 \times 10^{-6}$ M
390	> 50% inhibition at $1 \times 10^{-5}$ M
392	> 50% inhibition at $1 \times 10^{-5}$ M
399	> 50% inhibition at $1 \times 10^{-6}$ M
953	> 50% inhibition at $1 \times 10^{-6}$ M
955	> 50% inhibition at $1 \times 10^{-7}$ M
962	> 50% inhibition at $1 \times 10^{-7}$ M
964	> 50% inhibition at $1 \times 10^{-6}$ M
966	> 50% inhibition at $1 \times 10^{-6}$ M
967	> 50% inhibition at $1 \times 10^{-6}$ M
969	> 50% inhibition at $1 \times 10^{-5}$ M
974	> 50% inhibition at $1 \times 10^{-5}$ M

1395 Table 6. Inhibition of farnesyltransferase at concentrations of 10 mM and 1 mM unless specified as \* (0.1 mM) or \*\* (0.01 mM)

Example	% inhibition 10 mM	% inhibition 1 mM	Example	% inhibition 10 mM	% inhibition 1 mM
997		91**	1199		71
998		79**	1200		97*
999		90	1201		73*
1000		82*	1202		96**
1001		92**	1203		84*
1002		82**	1204		93*
1003		92*	1205		55**
1004		92**	1206		63**
1005		95**	1207		91*
1006		95**	1208		89*
1007		85**	1209		87*
1008		95**	1210		64**
1009		86**	1211		94
1010		90*	1212		86*

1011		92**	1213		79**
1012		88*	1214		92**
1013		80*	1215		17
1014		91	1216		88**
1015		59*	1217		87*
1016		92*	1218		54**
1017		51*	1219		85**
1018		97	1220		
1019		70	1221		82**
1020		39	1222		89*
1021		93*	1223		91**
1022		91**	1224		88*
1023		89**	1225		92**
1024		89**	1226		69**
1025		91**	1227		91
1026		74**	1228		88*
1027		81**	1229		66**
1028		92**	1230		77**
1029		82**	1231		93*
1030		92**	1232		68**
1031		90**	1233		77**
1032		93**	1234		71**
1033		76**	1235		86**
1034		77	1236		83**
1035		76	1237		89**
1036		79	1238		91**
1037		88	1239		85*
1038		57	1240		64**
1039		89**	1241		74*
1040		90**	1242		75*
1041		48	1243		95*
1042		88	1244		84
1043		90*	1245		92
1044		76*	1246		82

1045		86*	1247		95*
1046		93	1248		88
1047		95	1249		89
1048		78**	1250		79**
1049		93**	1251		91**
1050		62**	1252		84*
1051		79**	1253		76*
1052		91**	1254		67
1053		60**	1255		82*
1054		89**	1256		95*
1055		85**	1257		93**
1056		75**	1258		97**
1057		82*	1259		89**
1058		89	1260		90**
1059		92*	1261		94
1060		42	1262		95
1061		88*	1263		85*
1062		93	1264		83**
1063		92**	1265		90
1064		95**	1266		85*
1065		78*	1267		96
1066		73**	1268		95*
1067		93*	1269		84**
1068		79**	1270		91**
1069		74*	1271		78**
1070		93**	1272		73**
1071		95*	1273		94*
1072		82*	1274		89*
1073		93**	1275		86**
1074		82	1276		88**
1075		90**	1277		90**
1076		69**	1278		68
1077		93**	1279		87**
1078		86*	1280		78**

1079		90	1281		81*
1080		87	1282		69*
1081		61	1283		74*
1082		84*	1284		86
1083		88	1285		94
1084		76**	1286		85**
1085		93*	1287		95**
1086		87*	1288		69*
1087		76*	1289		93
1088		73*	1290		80
1089		86*	1291		
1090		81**	1292		
1091		87*	1293		
1092		74**	1294		
1093		95**	1295		
1094		96**	1296		
1095		76*	1297		
1096		86*	1298		97**
1097		80**	1299		96**
1098		60*	1300		97*
1099		87**	1301		97*
1100		82**	1302		93**
1101		86*	1303		91**
1102		84**	1304		90**
1103		92*	1305		91**
1104		89**	1306		85**
1105		91**	1307		85**
1106		67**	1308		91**
1107		88**	1309		96*
1108		95**	1310		90**
1109		74**	1311		95**
1110			1312		91**
1111		63**	1313		91**
1112		62	1314		96*

1113		55	1315		86*
1114		83**	1316		78*
1115		94*	1317	99	96
1116		91**	1318		
1117		92*	1319		79**
1118		86*	1320		79
1119		84**	1321		
1120		93	1322		
1121		72*	1323		
1122		92**	1324		
1123		90*	1325		
1124		90*	1326		
1125		92*	1327		
1126		87	1328		
1127		90*	1329		
1128		86*	1330		
1129		92**	1331		
1130		88**	1332		92**
1131		96**	1333		95*
1132		97*	1334		72**
1133		75*	1335		90*
1134		95**	1336		74
1135		88*	1337		83**
1136		91	1338		65*
1137		83**	1339		
1138		65*	1340		77*
1139		92*	1341		89
1140		77**	1342		
1141		80*	1343		88
1142		84**	1344		93**
1143		92*	1345		94**
1144		76*	1346		94*
1145		83*	1347		81**
1146		61**	1348		78**

1147		93*	1349		92**
1148		79**	1350		
1149		94*	1351		
1150		92*	1352		
1151		91*	1353		
1152		96*	1354		38
1153		89*	1355		46
1154		93*	1356		80
1155		91*	1357		78
1156		87	1358		
1157		66**	1359		
1158	75		1360		98**
1159		72*	1361		96*
1160		83*	1362		83**
1161		87*	1363		88**
1162		84*	1364		
1163		73**	1365		
1164		94	1366		79*
1165		84*	1367		93*
1166		74**	1368		92**
1167		91*	1369		94*
1168		88*	1370		86**
1169		77	1371		94*
1170		74*	1372		95**
1171		74**	1373		95**
1172		38*	1374		93**
1173		89**	1375		80**
1174		79**	1376		86**
1175		96	1377		95*
1176		97*	1378		68
1177		19	1379		41
1178		88**	1380		87**
1179		85*	1381		65**
1180		93*	1382		86**

1181		82*	1383		88*
1182		92**	1384		69**
1183		79**	1385		93*
1184		84**	1386		88*
1185		85**	1387		82**
1186		93**	1392		93*
1187		93**	1397		87**
1188		93**	1398		81*
1189		74**	1399		94
1190		95**	1400		95
1191		85**			
1192		91*			
1193		95**			
1194		78**			
1195		94*			
1196		87*			
1197		85*			
1198		86*			

\* % inhibition at 0.1  $\mu$ M

\*\* % inhibition at 0.01  $\mu$ M

1400 Additional methods for the measurement of *in vitro* inhibition of protein prenylation (i.e., inhibition of farnesyltransferase or geranygeranyltransferase) are described below.

Assays are performed using the glass fiber filter binding assay procedure with either rabbit reticulocyte lysate or FTase or GGTase I fractions isolated from bovine brains using a combination of hydrophobic and DEAE column chromatography procedures. Protein  
 1405 substrates are purchased from Panvera Corporation (H-ras for FTase, H-ras-CVLL for GGTase I). Tritium labeled prenyl lipid substrates (FPP or GGPP) are obtained from Amersham Life Science.

#### FTase

1410  $^3$ H-Farnesyldiphosphate (final concentration 0.6  $\mu$ M), H-Ras (final concentration 5.0  $\mu$ M) and the test compound (various final concentrations from a stock solution in 50% DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM HEPES (pH 7.5), 30 mM  $MgCl_2$ , 20 mM KCl, 10  $\mu$ M  $ZnCl_2$ , 5 mM DTT, 0.01% Triton X-100) to give



a final volume of 50  $\mu$ L. The mixture was brought to 37 °C, enzyme was added, and the  
1415 reaction is incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the  
reaction, and the mixture was allowed to stand for 15 minutes at room temperature then  
diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass  
microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass  
filter was transferred to a scintillation vial and 5 mL of scintillation fluid was added. The  
1420 radioisotope retained on the glass fiber filter was counted to reflect the activity of the  
enzymes. The IC<sub>50</sub> value was calculated by measuring the activity of the enzyme over a  
suitable range of inhibitor concentrations.

#### GGTase I

1425 <sup>3</sup>H-geranylgeranyldiphosphate (final concentration 0.5  $\mu$ M), H-Ras-CVLL (final  
concentration 5.0  $\mu$ M) and the test compound (various final concentrations from a stock  
solution in 1:1 DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50  
mM Tris-HCl (pH 7.2), 30 mM MgCl<sub>2</sub>, 20 mM KCl, 10  $\mu$ M ZnCl<sub>2</sub>, 5 mM DTT, 0.01%  
Triton X-100) to give a final volume of 50  $\mu$ L. The mixture was brought to 37 °C, treated  
1430 with enzyme, and incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the  
reaction, and the mixture was allowed to stand for 15 minutes at room temperature then  
diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass  
microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass  
filter was transferred to a scintillation vial, and 5 mL scintillation fluid was added. The  
1435 radioisotope retained on the glass fiber filter was counted to reflect the activity of the  
enzymes. The IC<sub>50</sub> value was calculated by measuring the activity of the enzyme over a  
suitable range of inhibitor concentrations.

Additionally, the ability of the compounds of the invention to inhibit prenylation in  
whole cells, inhibit anchorage-independent tumor cell growth and inhibit human tumor  
1440 xenograft in mice could be demonstrated according to the methods described in PCT Patent  
Application No. WO95/25086, published September 21, 1995, which is hereby  
incorporated herein by reference.

#### Pharmaceutical Compositions

1445 The compounds of the present invention can be used in the form of pharmaceutically  
acceptable salts derived from inorganic or organic acids. These salts include, but are not  
limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate,  
benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate,  
cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate,  
1450 glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride,

hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be  
1455 quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

1460 Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification  
1465 of the compounds of formula (I)-(XII) or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals such as sodium, lithium, potassium, calcium, magnesium,  
1470 aluminum salts and the like as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine,  
1475 piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein isoprenyltransferases (i.e, protein farnesyltransferase and/or protein geranylgeranyltransferase) and the isoprenylation (i.e., farnesylation and/or geranylgeranylation) of Ras. These inhibitors of protein isoprenyltransferases are also  
1480 useful for inhibiting or treating cancer in humans and other mammals. Examples of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas such as lung, colorectal, bladder, breast, kidney, ovarian, liver, exocrine pancreatic, cervical, esophageal, stomach and small intestinal; sarcomas such as osteosarcoma, osteoid sarcoma, lipoma, liposarcoma, hemangioma and hemangiosarcoma; melanomas such as  
1485 amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma and Hodgkins disease and leukemias, such as

myeloid, acute lymphoblastic, chronic lymphocytic, acute myeloblastic and chronic myelocytic.

The ability of the compounds of the invention to inhibit or treat cancer can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., *Drugs Exptl. Clin. Res.* 13(6), 345-351 (1987) Bissery, M.C., Guenard F., Gueritte-Voegelein F., Lavelle F., *Cancer Res.* 51, 4845-4852 (1991) and Rygaard J., and Povlsen C., *Acta Pathol. Microbiol. Scand.* 77, 758 (1969), which are hereby incorporated herein by reference.

These inhibitors of protein isoprenyltransferases are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to treat or prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. *Circ. Res.* 73: 264-268 (1993), Mitsuka, M. et al. *Circ. Res.* 73: 269-275 (1993) and Santoian, E.C. et al. *Circulation* 88: 11-14 (1993), which are hereby incorporated herein by reference.

For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

1525           Injectable preparations, for example sterile injectable aqueous or oleagenous suspensions, may be formulated according to the known art using suitable dispersing or wetting and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (as in a solution in 1,3-propanediol, for example). Among the acceptable vehicles and solvents  
1530 that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Additionally, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the  
1535 drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed  
1540 with at least one inert diluent such as sucrose, lactose or starch. These dosage forms may also comprise additional substances other than inert diluents such as lubricating agents like magnesium stearate. With capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills may also be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable  
1545 emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents, emulsifying and suspending agents and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of  
1550 liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers,  
1555 preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, which is hereby incorporated herein by reference.



1560 While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described in Holleb, et al., Clinical Oncology, American Cancer Society, United States (1991) p 56 *et seq.*, which is  
1565 hereby incorporated herein by reference. These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethylenimines (thiotepa, hexamethylmelamine); folic acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside);  
1570 purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine and vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin, taxol and brequinar).

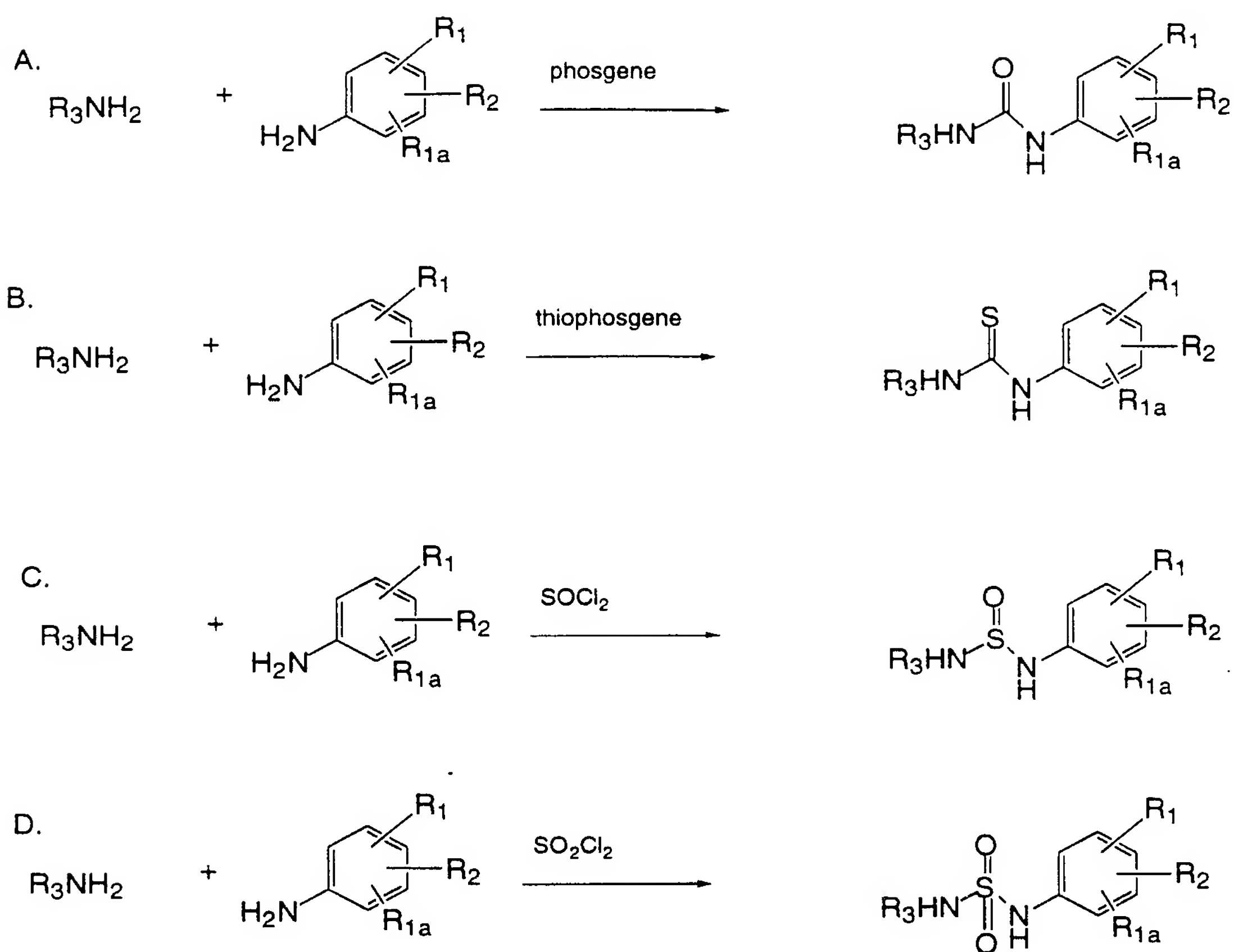
1575 The above compounds to be employed in combination with the isoprenyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by reference or by such therapeutically useful amounts as would be known to one of ordinary skill in the art.

1580 The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient.

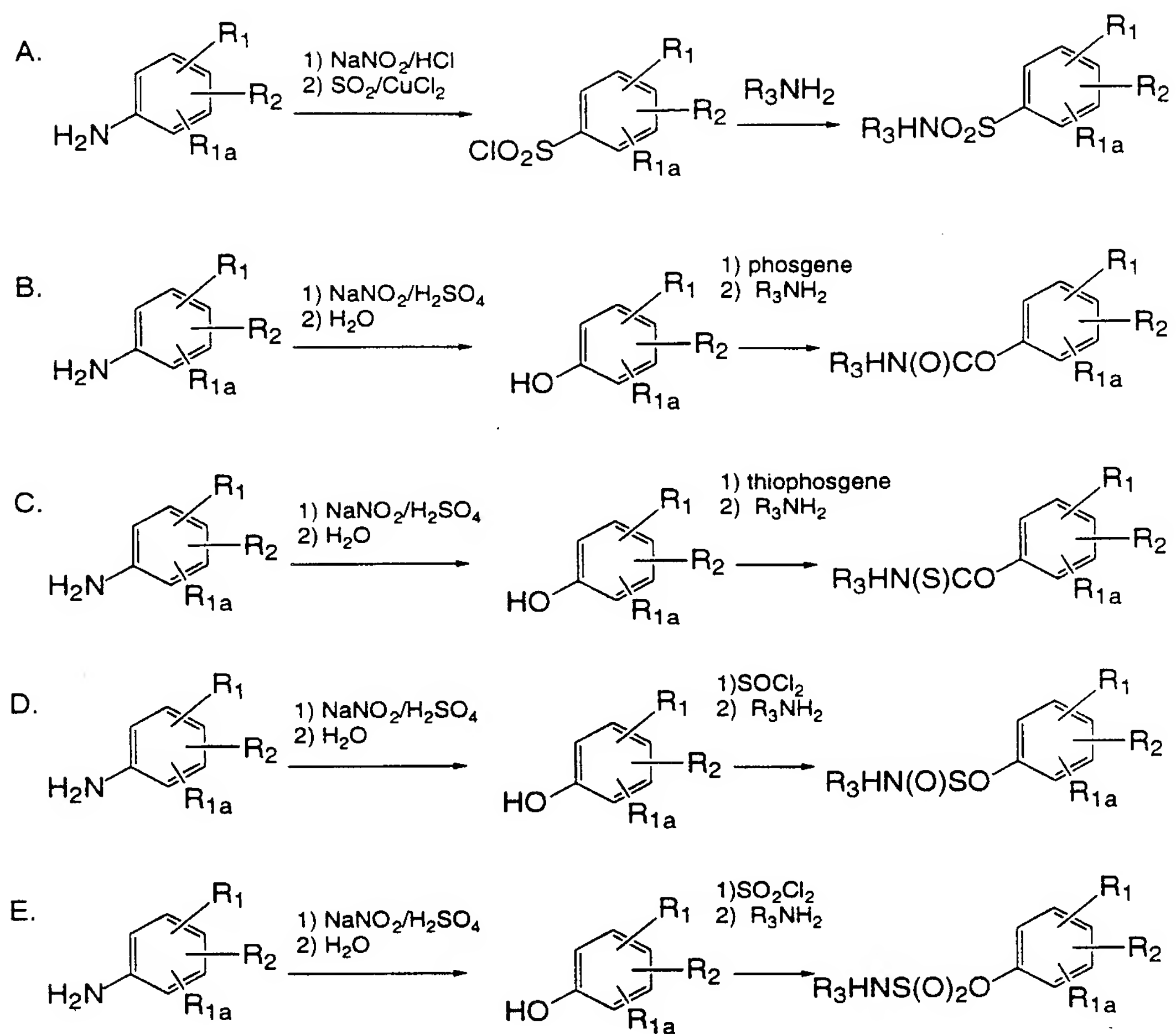
1585 When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

#### Preparation of the Compounds of the Invention

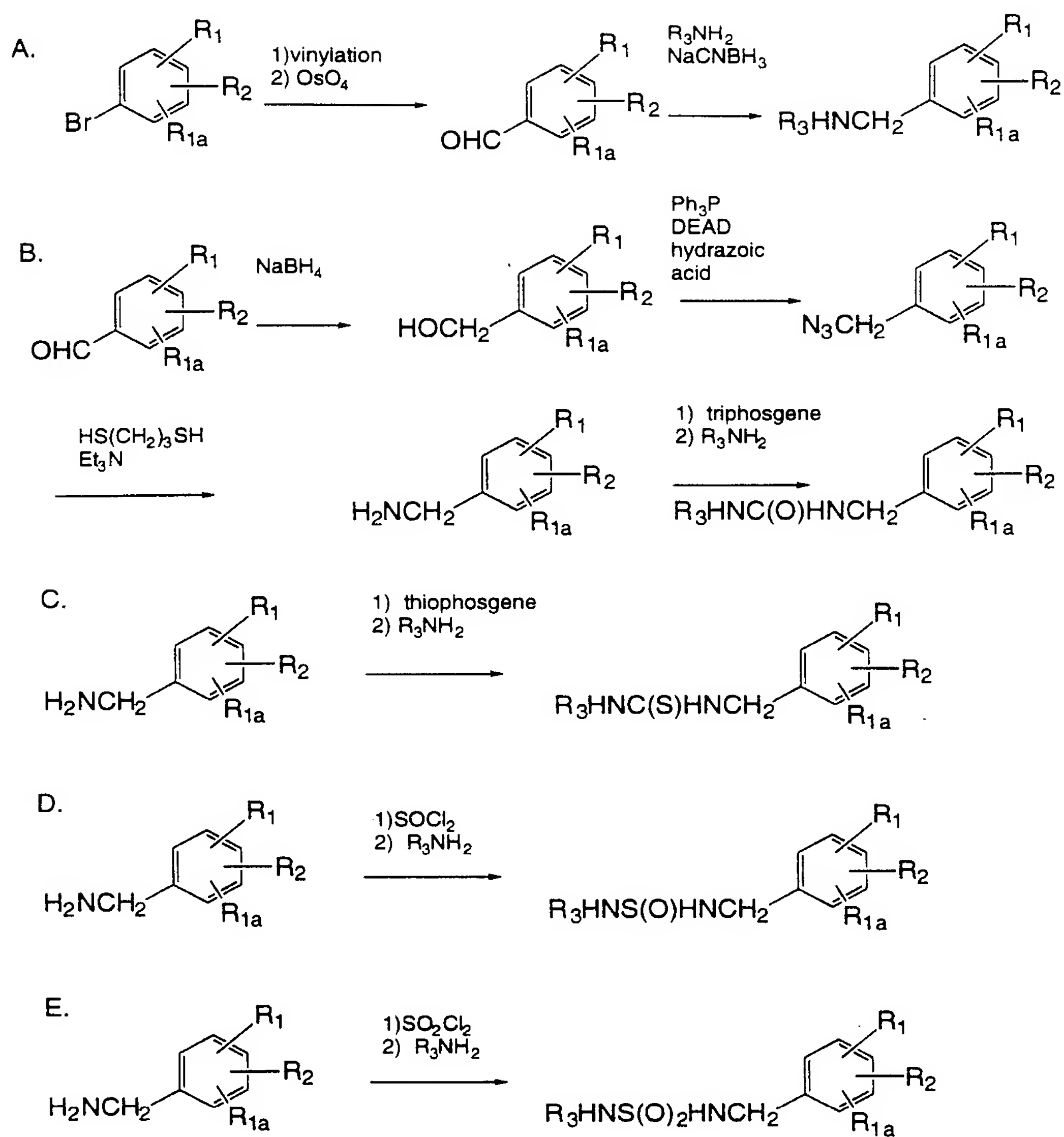
1590 In general, the compounds of the invention can be prepared by the processes illustrated in the following Schemes 1-16. In these general schemes compounds of the formula I are used to exemplify the methods, but the methods are intended to be applicable to all of the compounds of the invention.

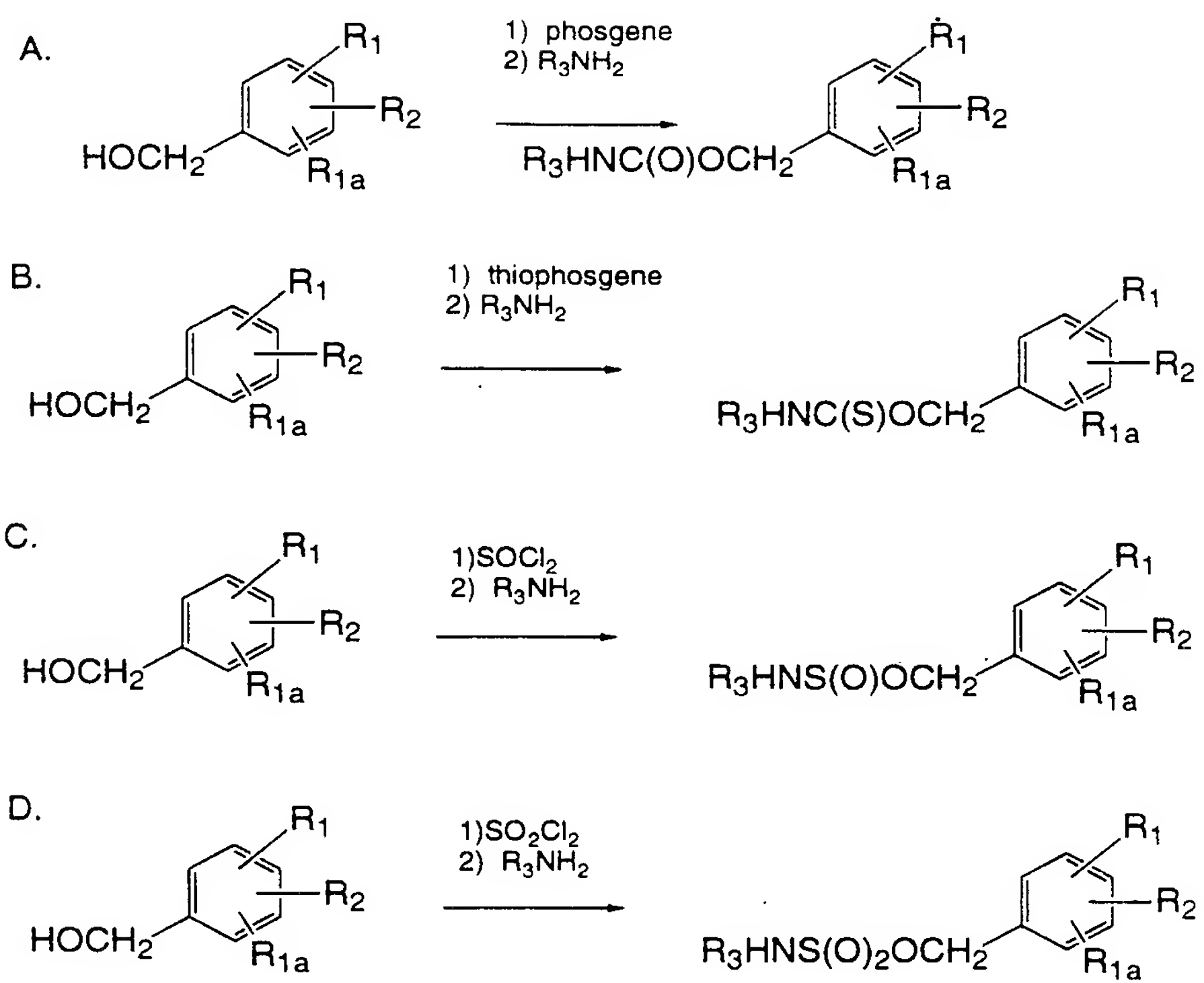
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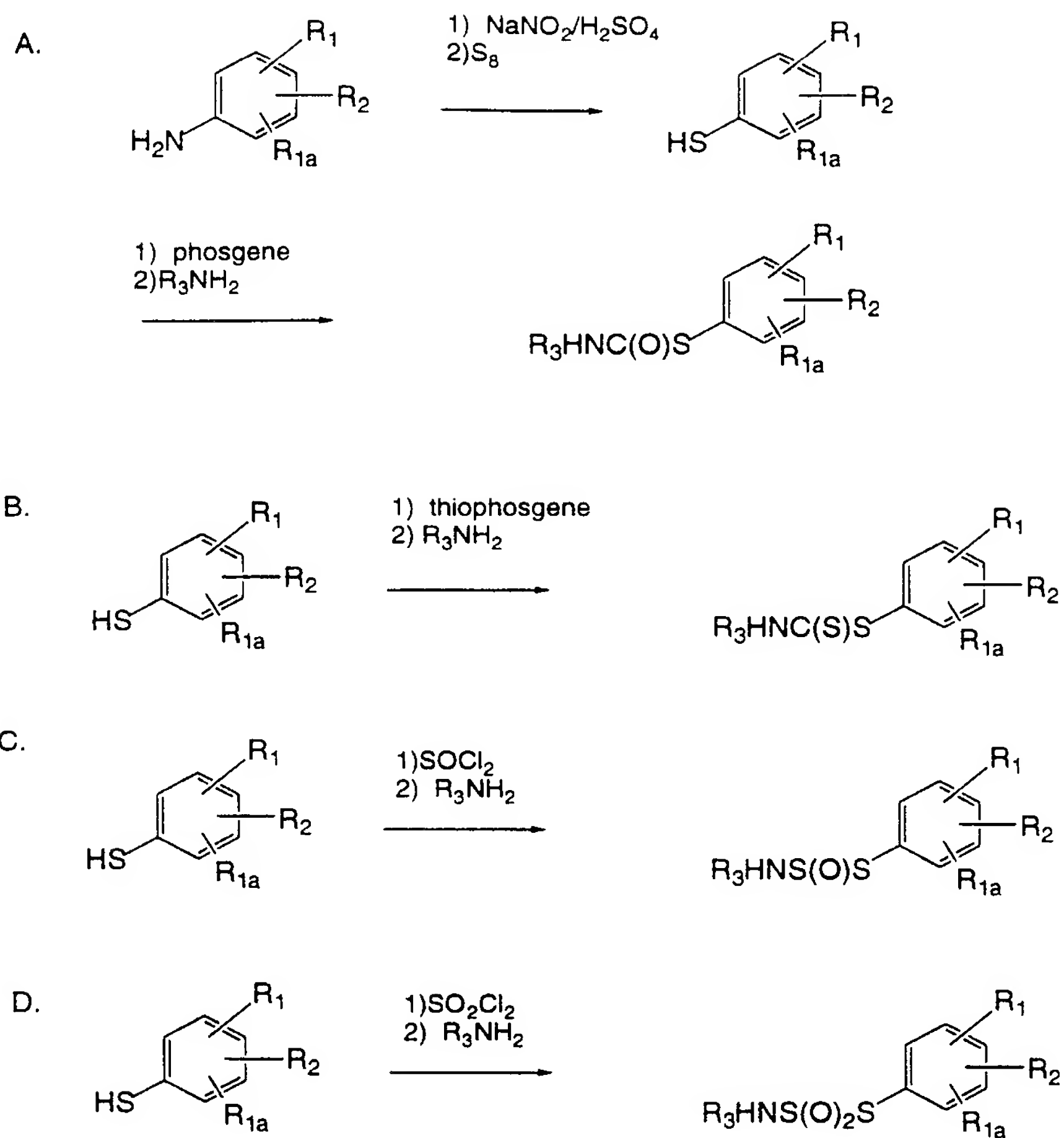
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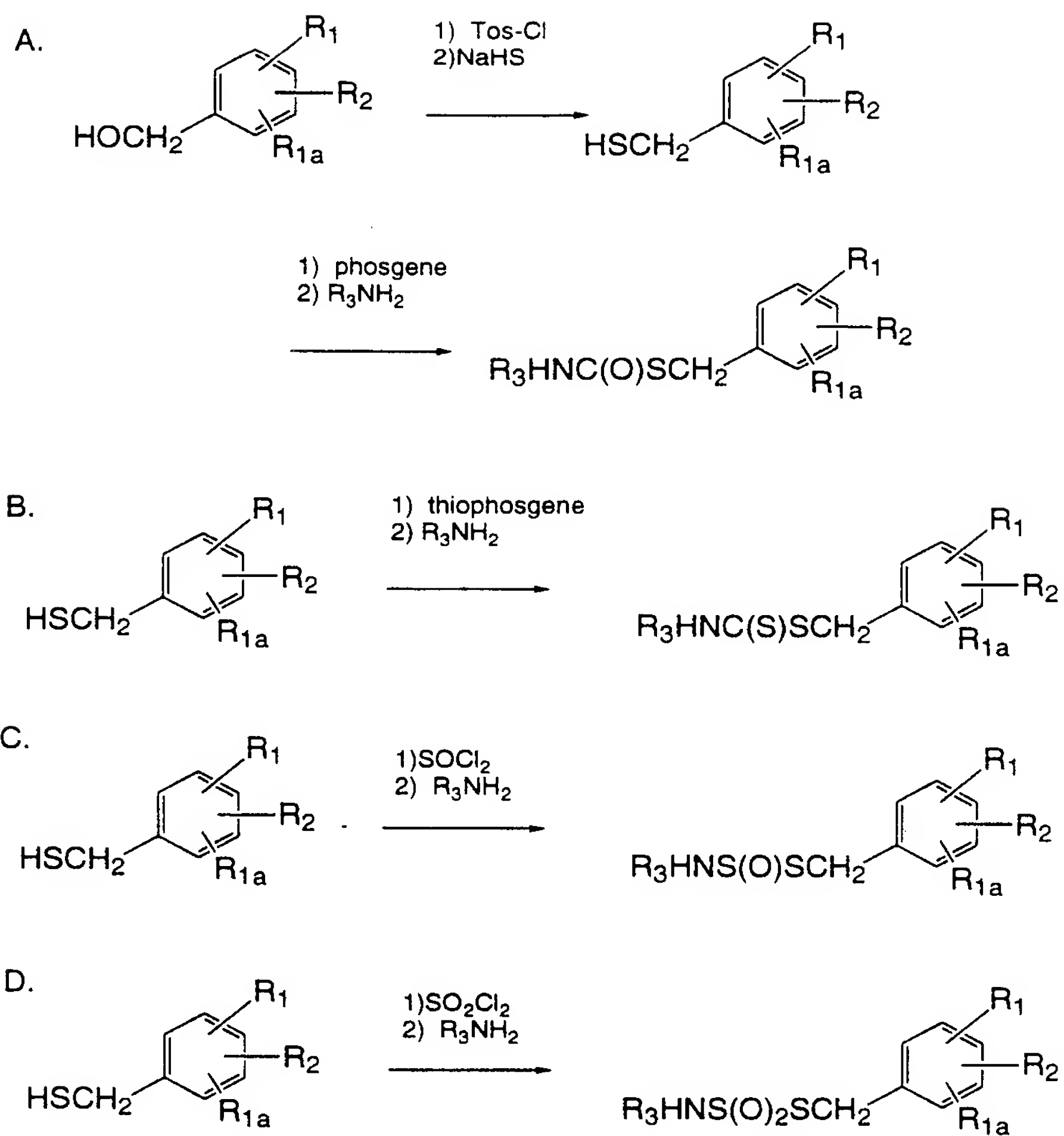
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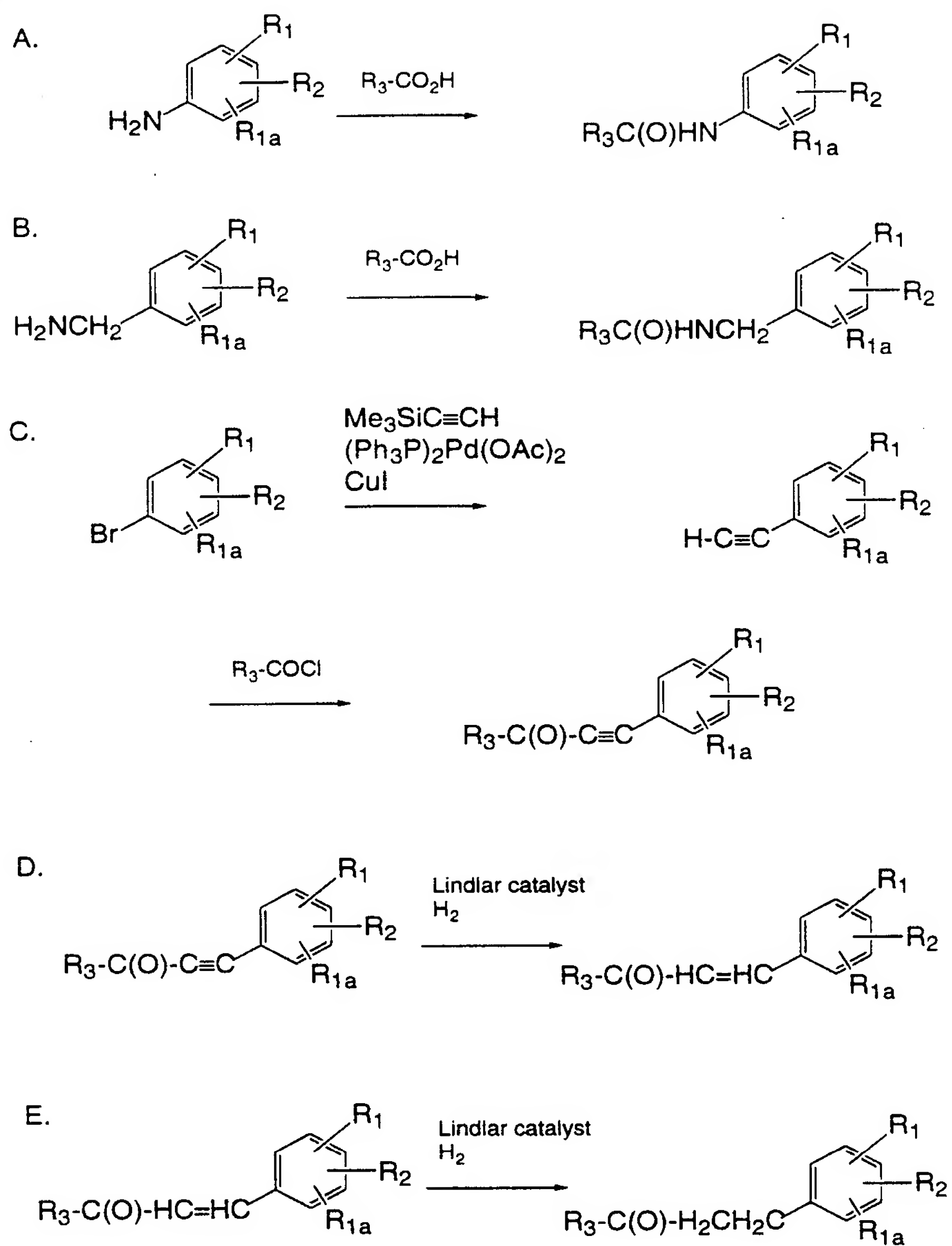


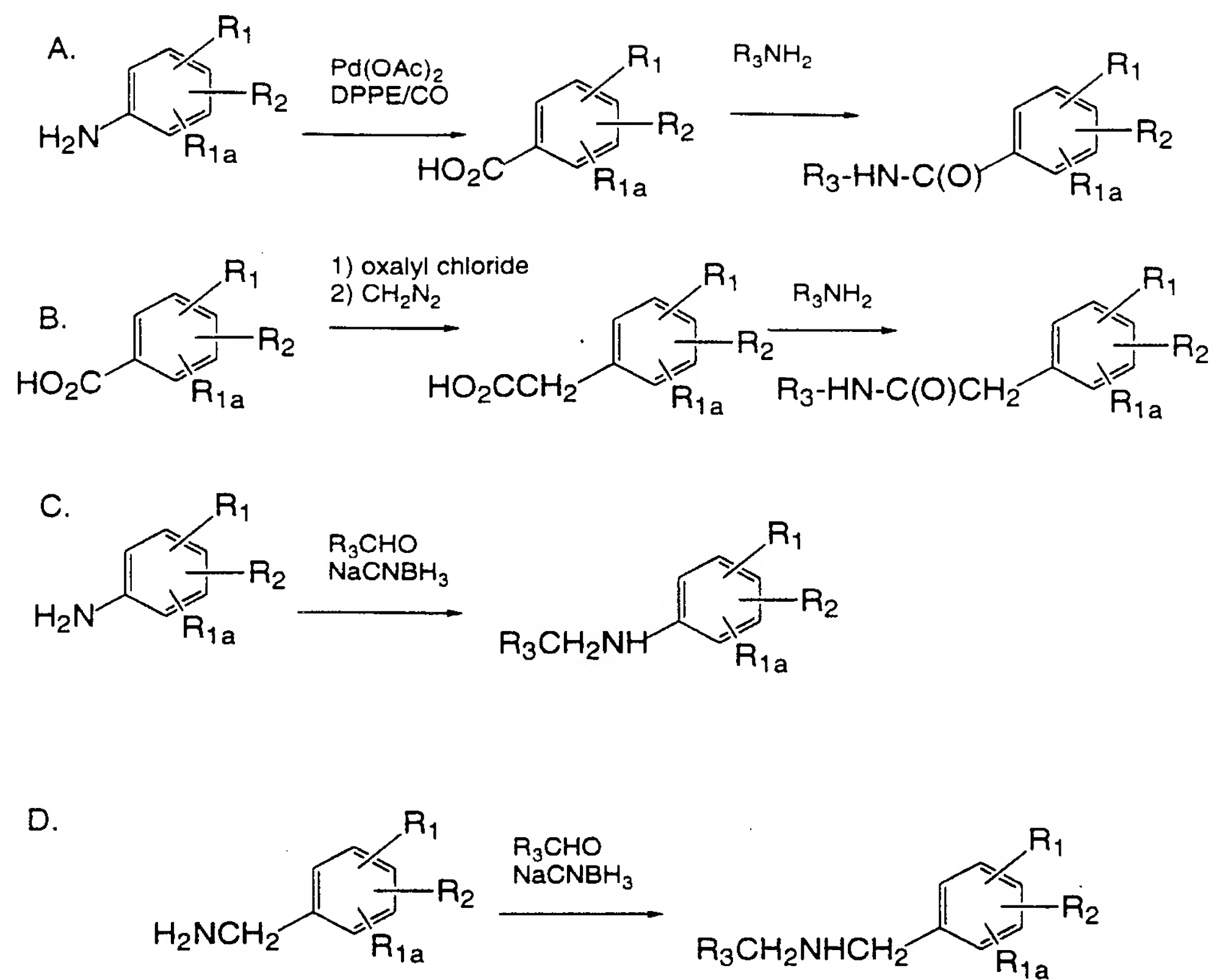
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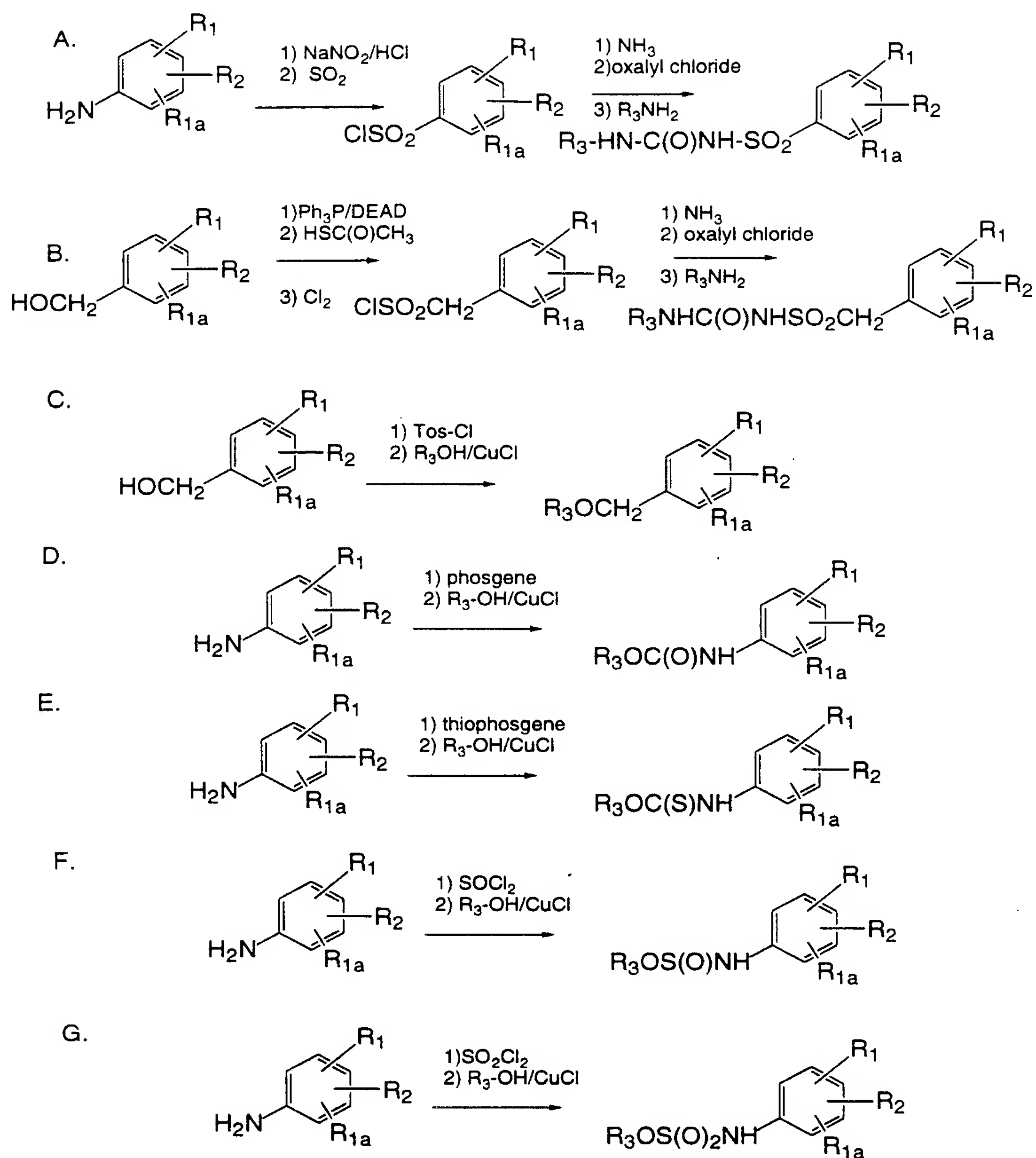
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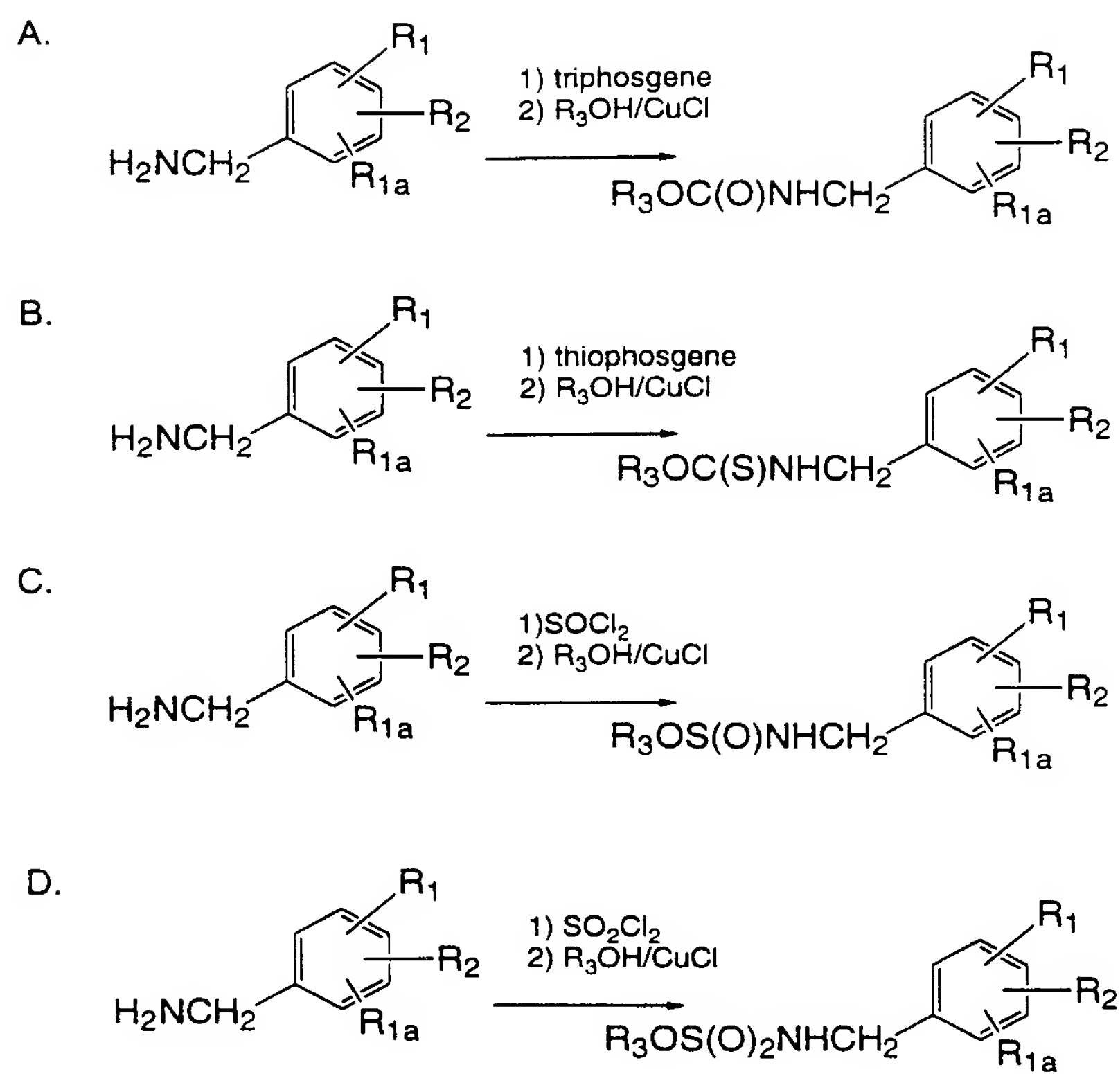
**SCHEME 5**

**SCHEME 6**

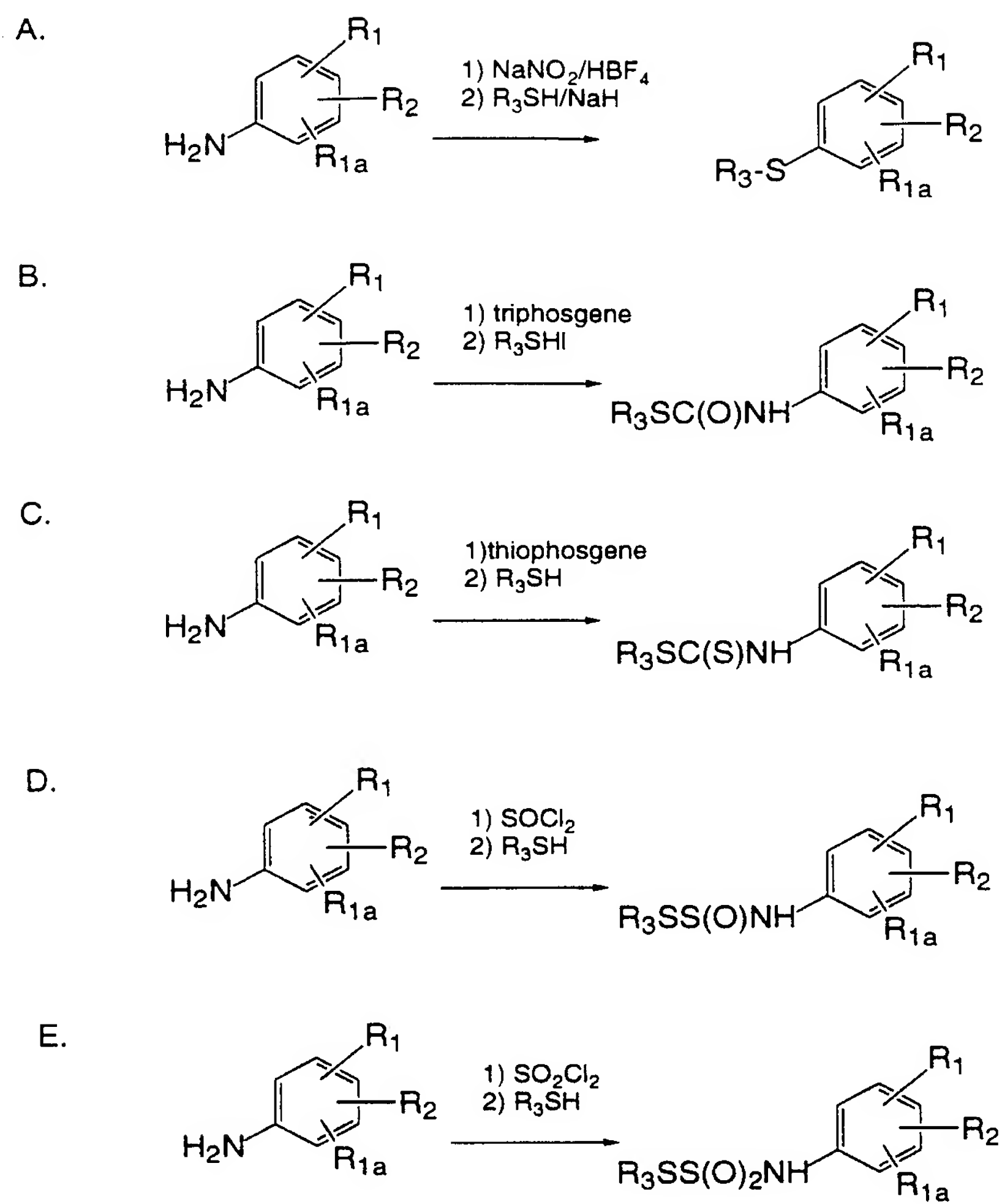
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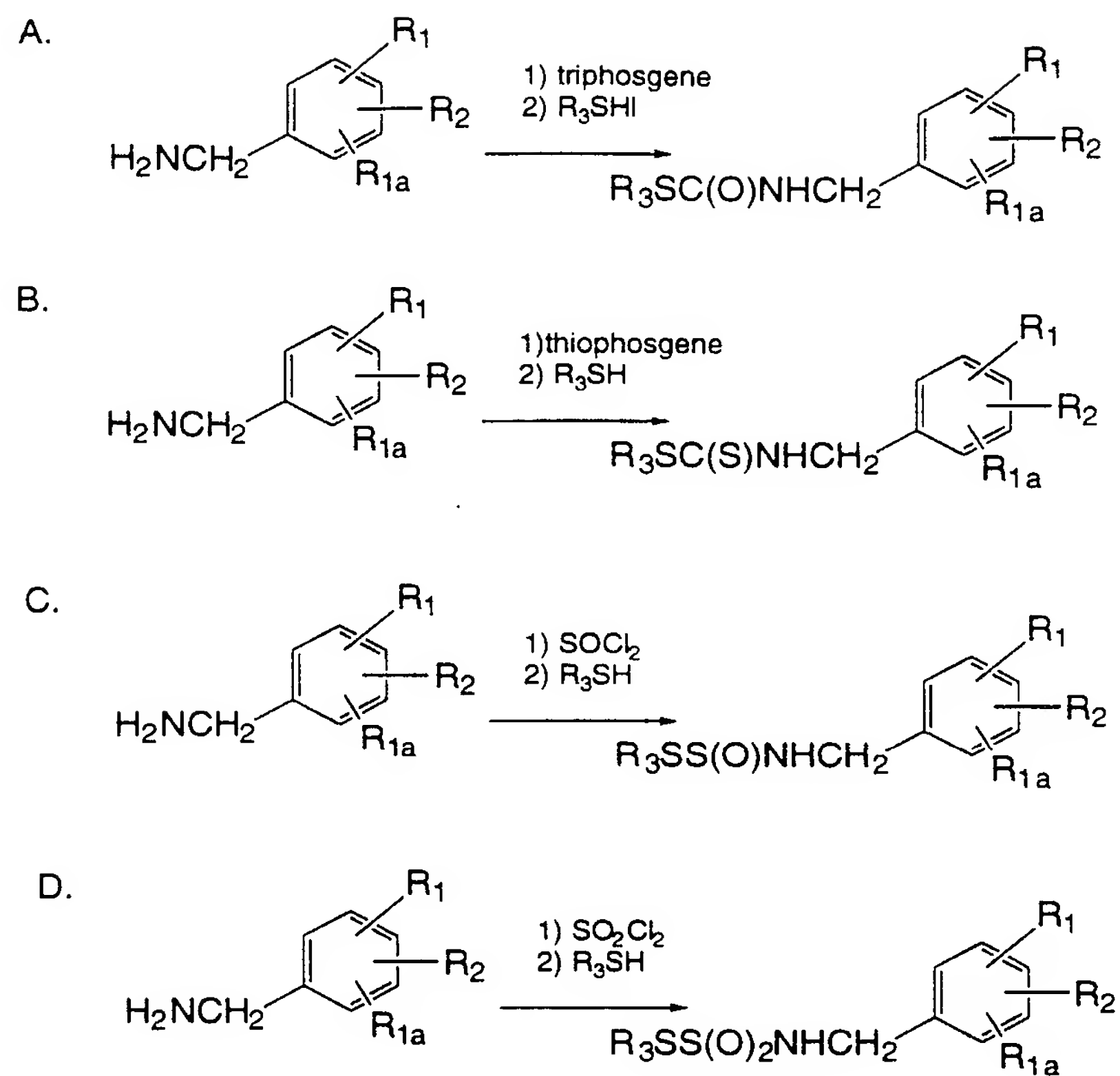
**SCHEME 8**

**SCHEME 9**

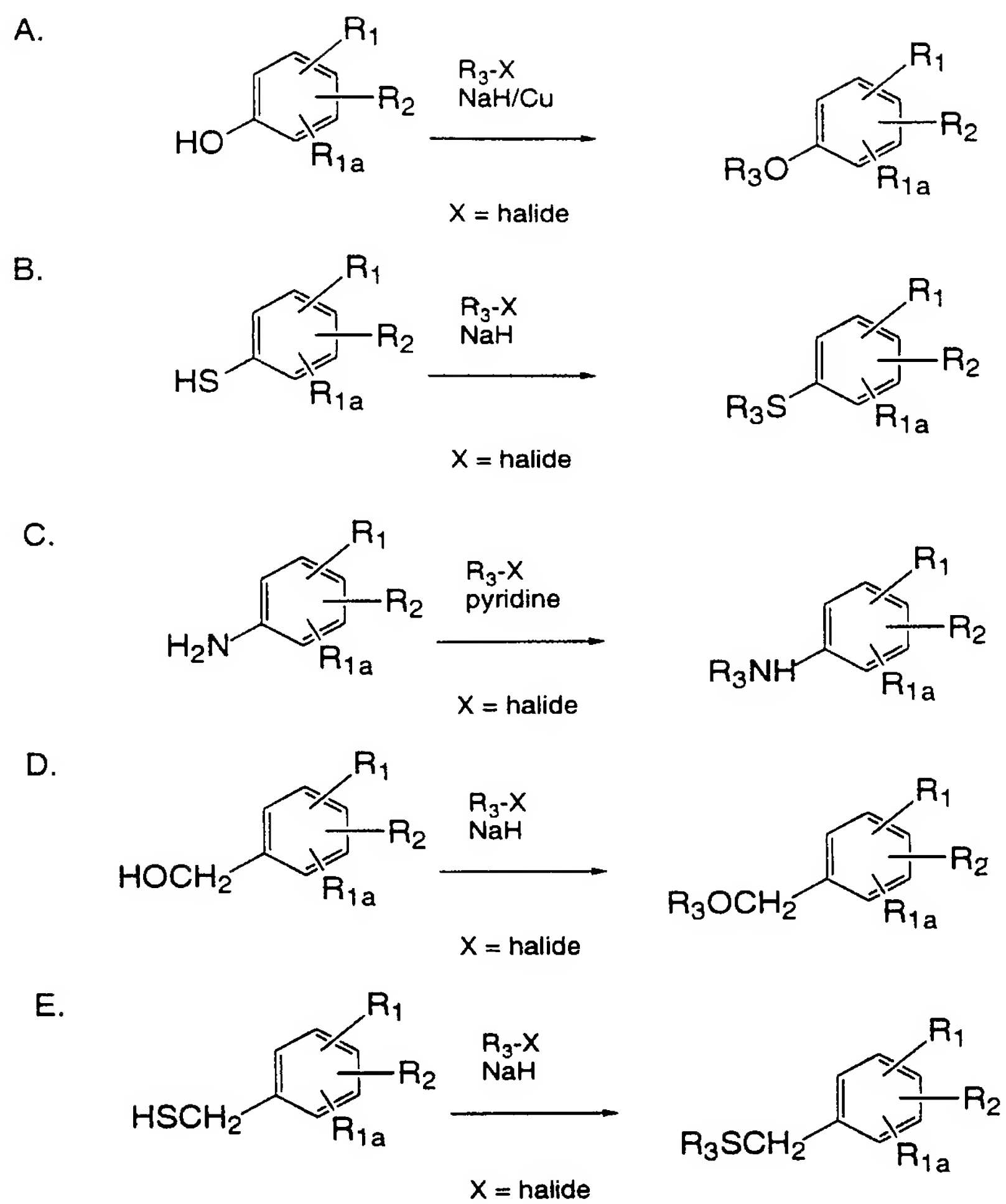
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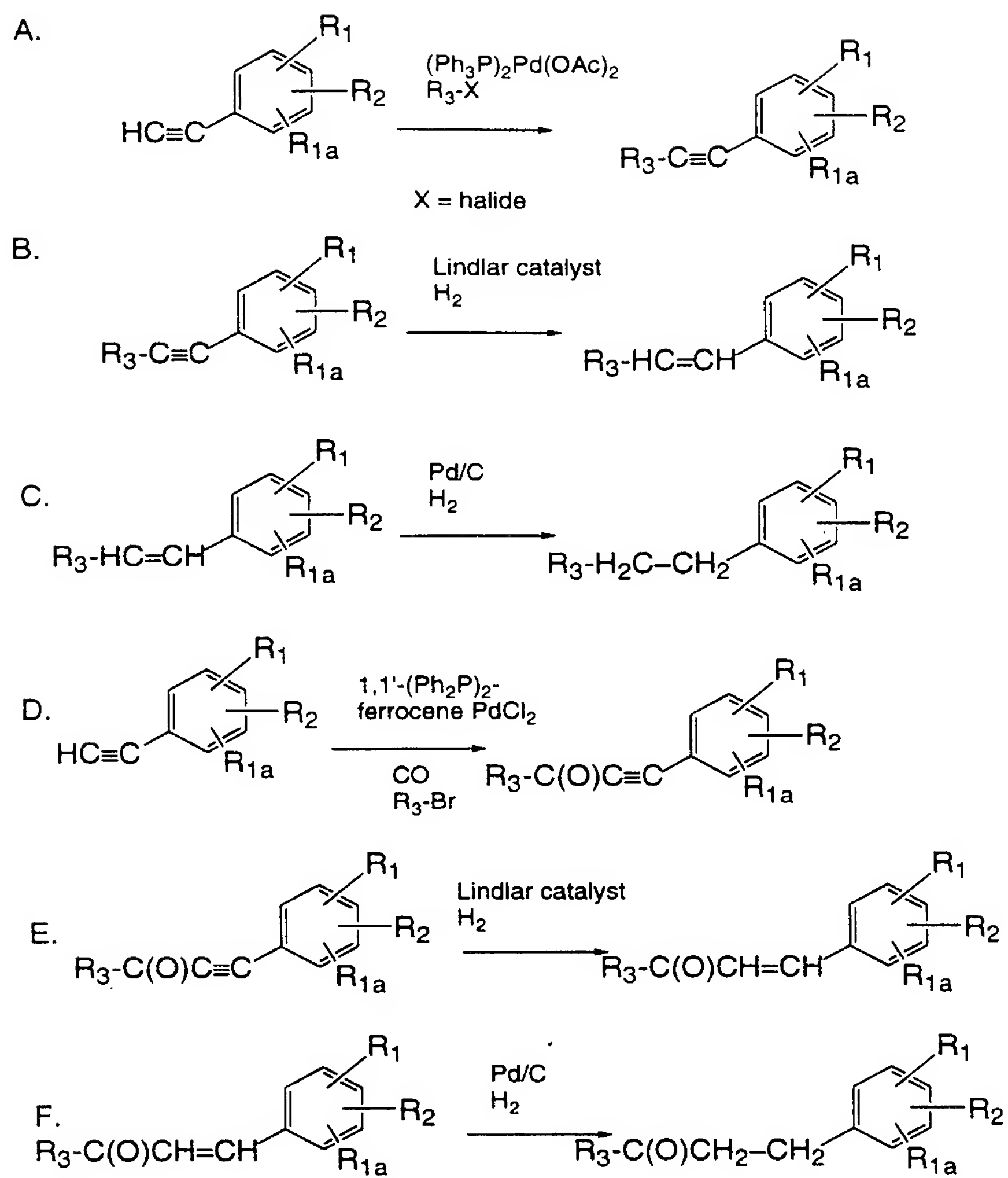


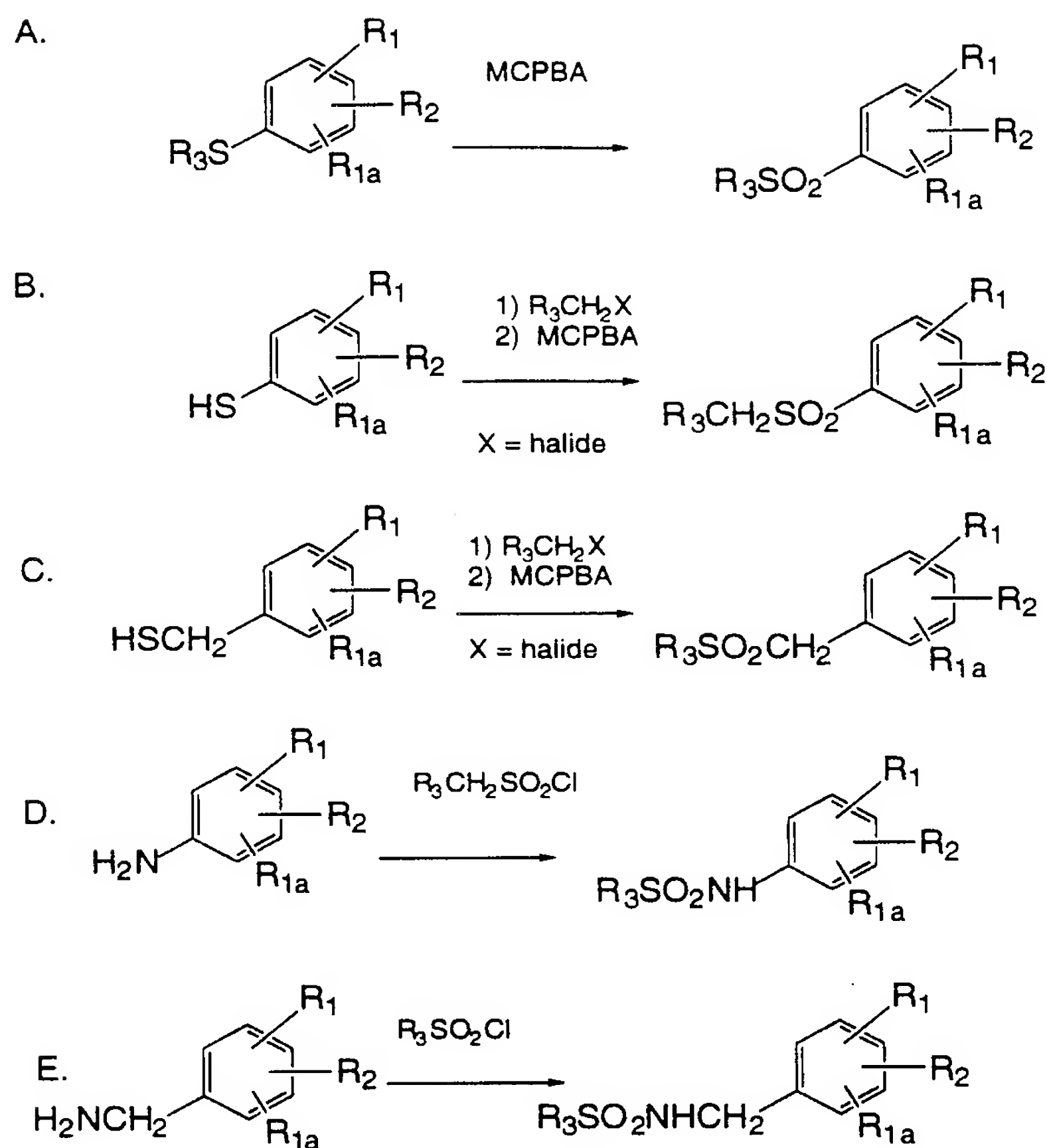
**SCHEME 11**

**SCHEME 12**

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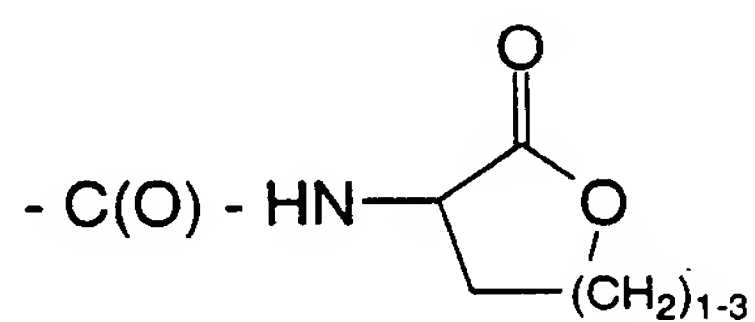
**SCHEME 13**

**SCHEME 14**

**SCHEME 15**

1635

Scheme 16 illustrates an alternative method for preparing compounds wherein  $R_2$  is  $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(\text{O})\text{OR}_{15}$  or



1640 as defined above.

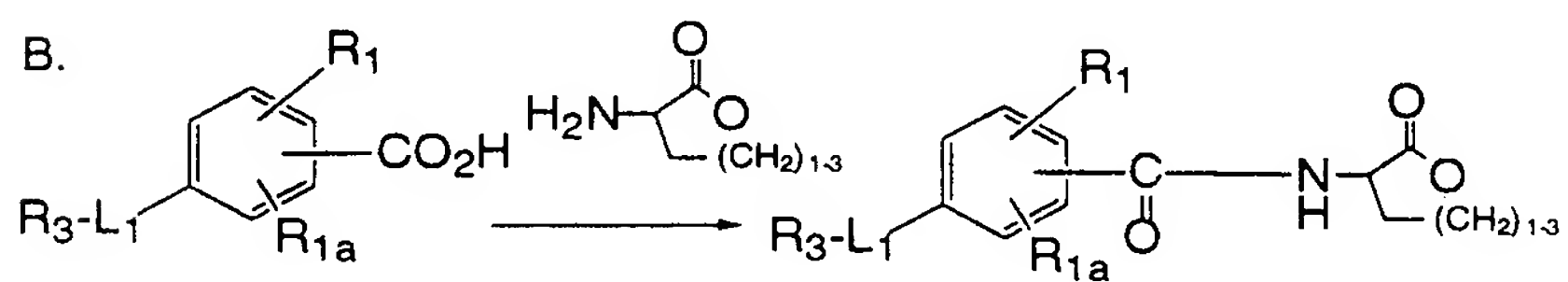
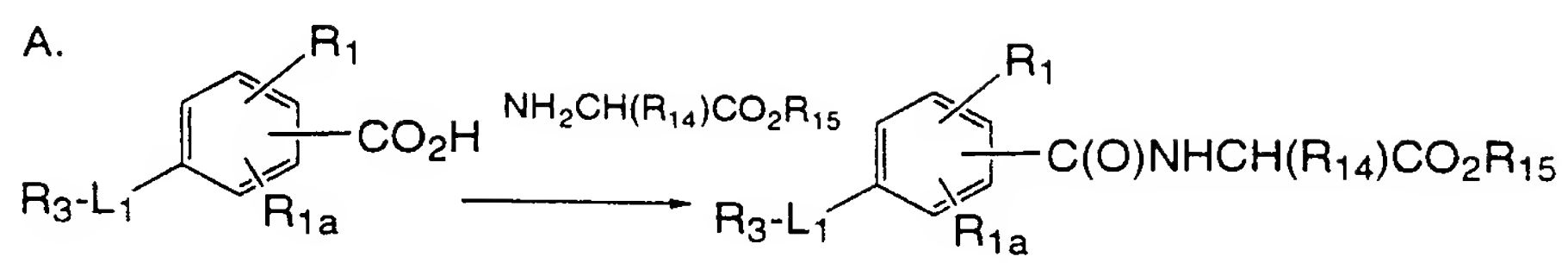
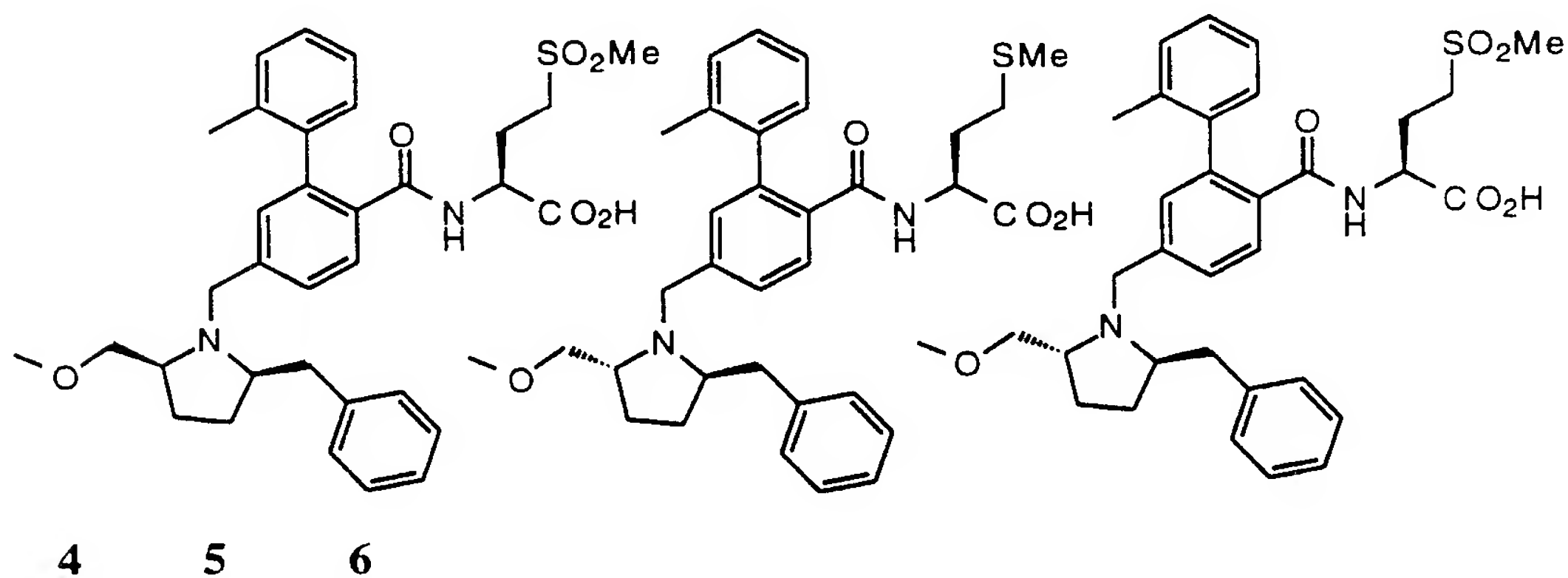
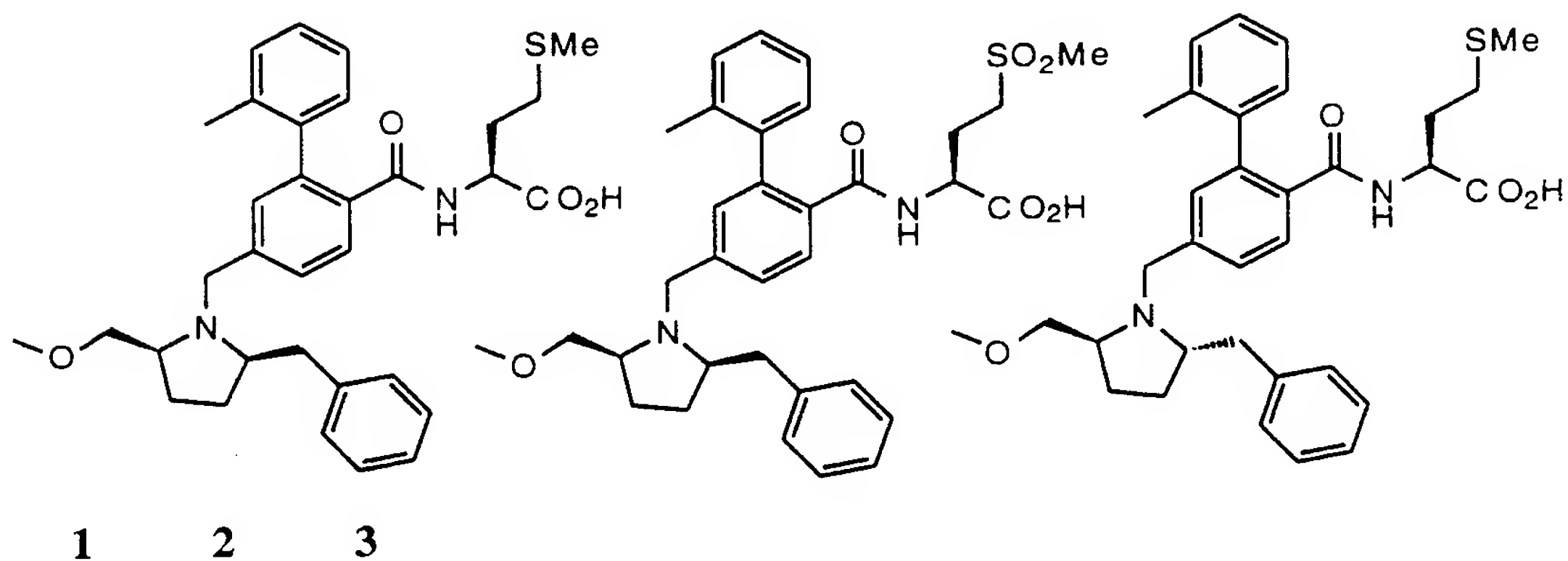
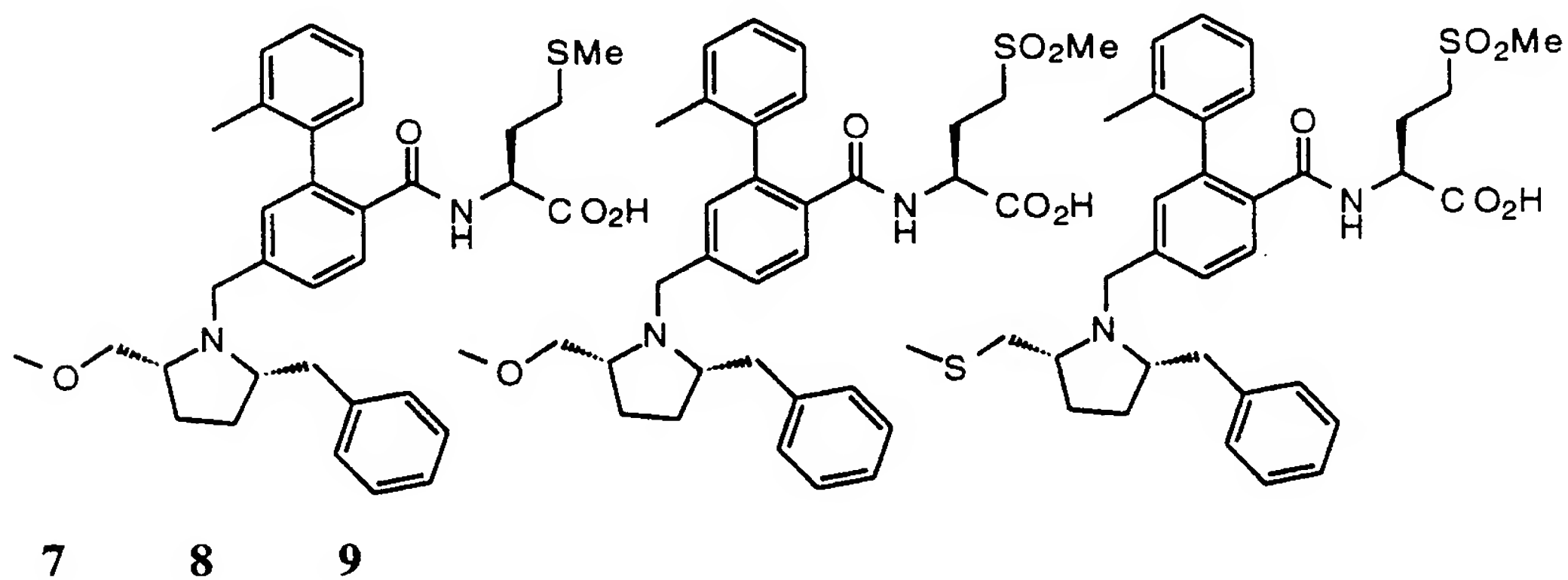
**SCHEME 16**

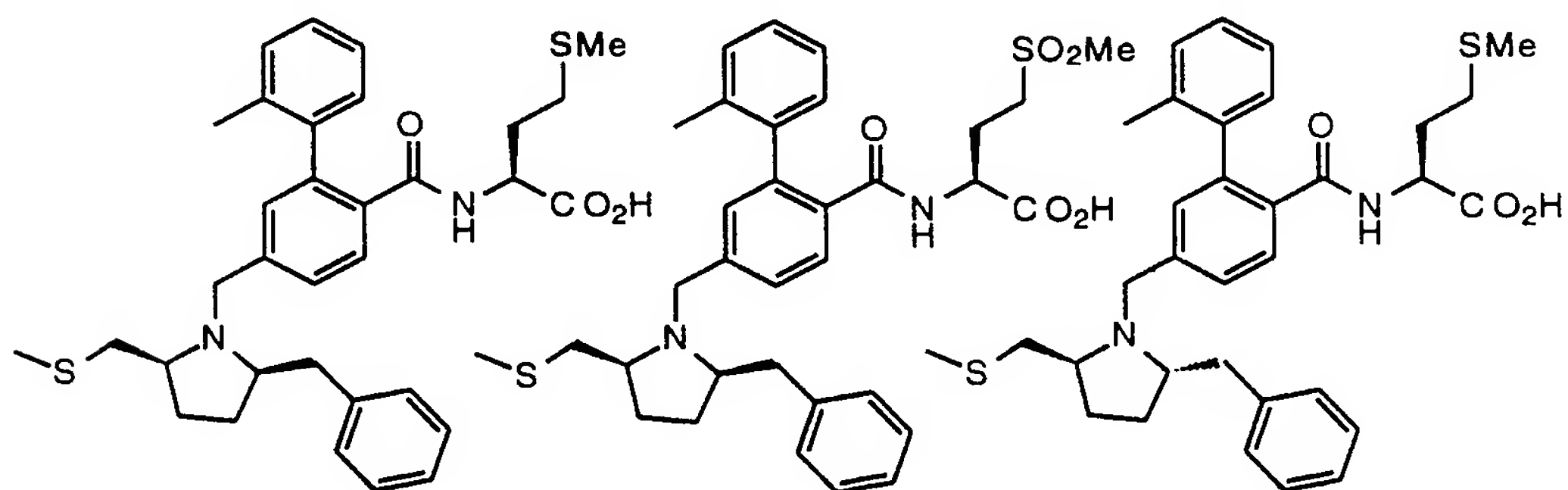
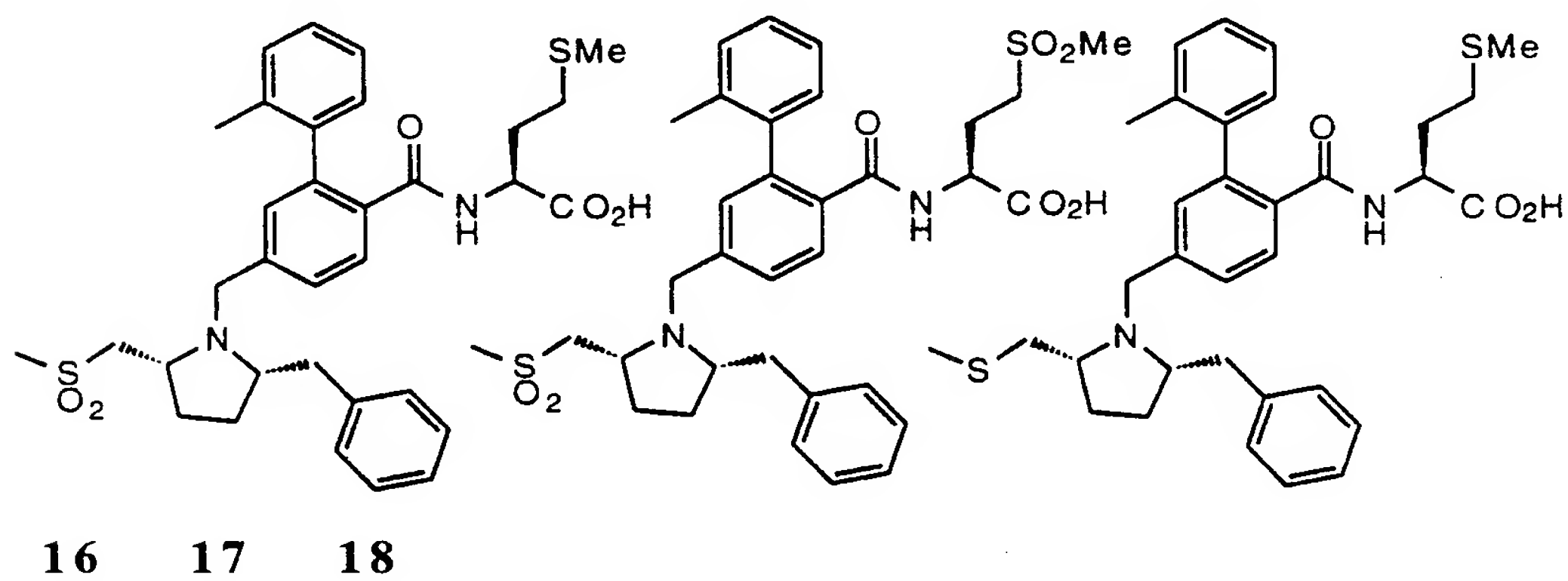
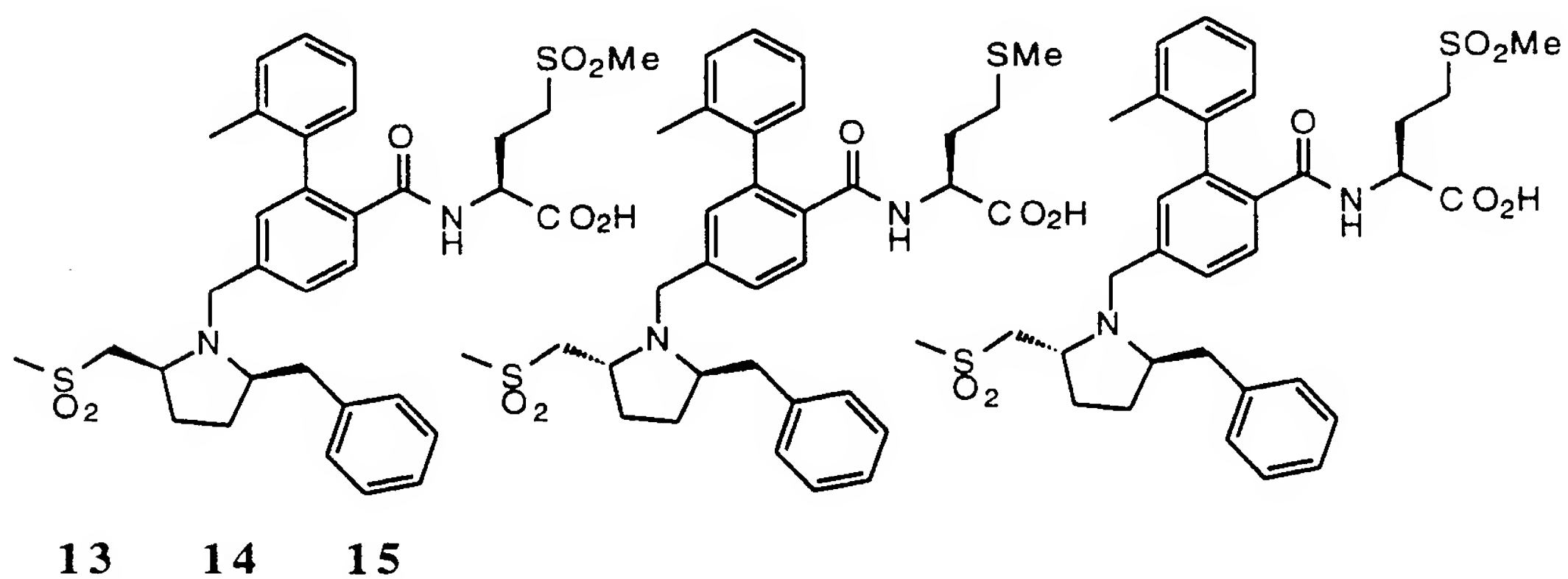
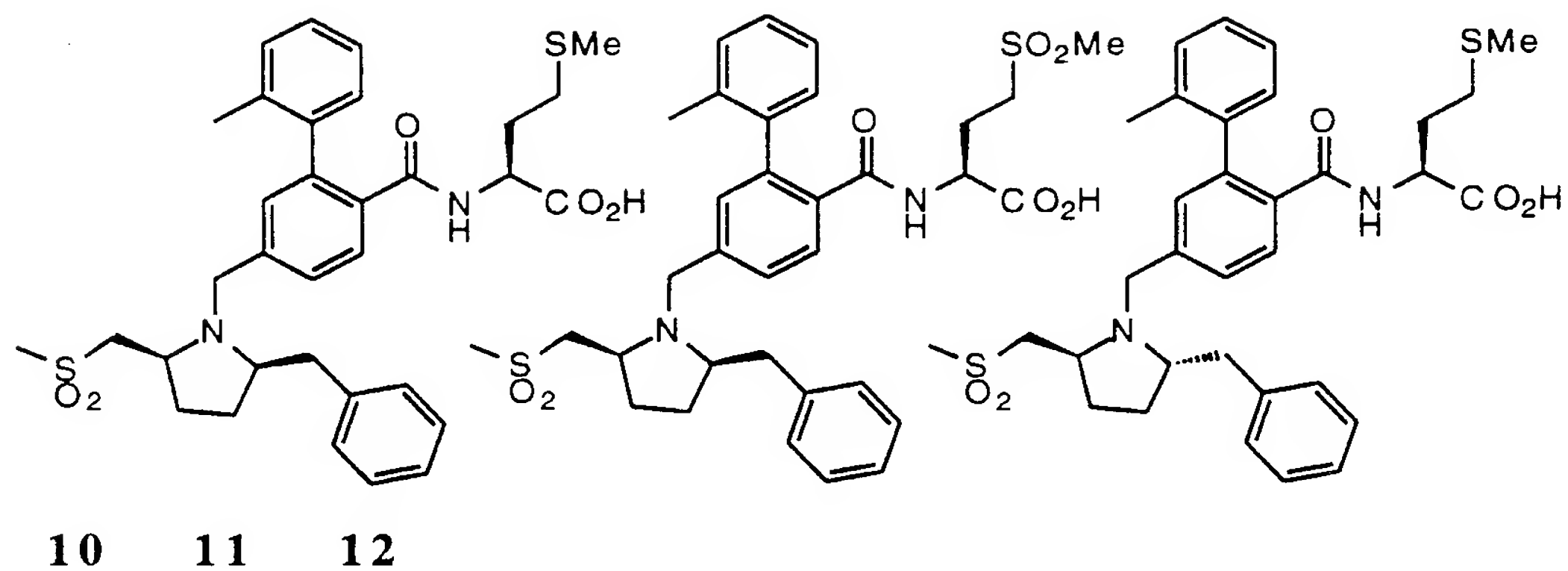
Table 6. Amines of the Type A(B)N-L<sub>1</sub>

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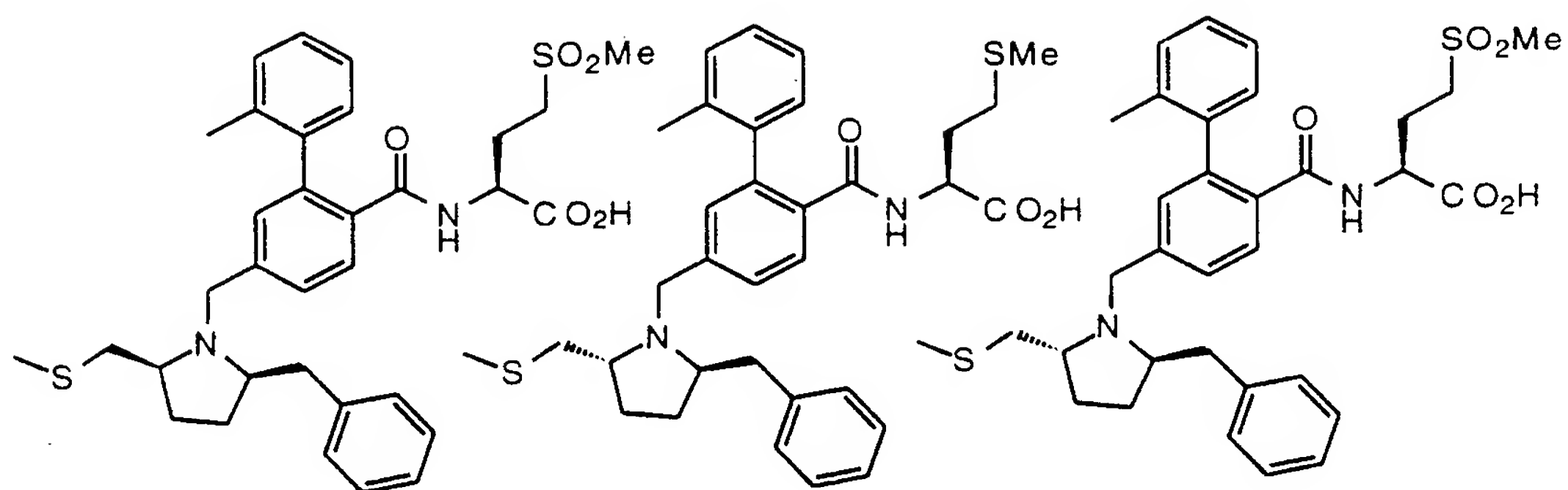




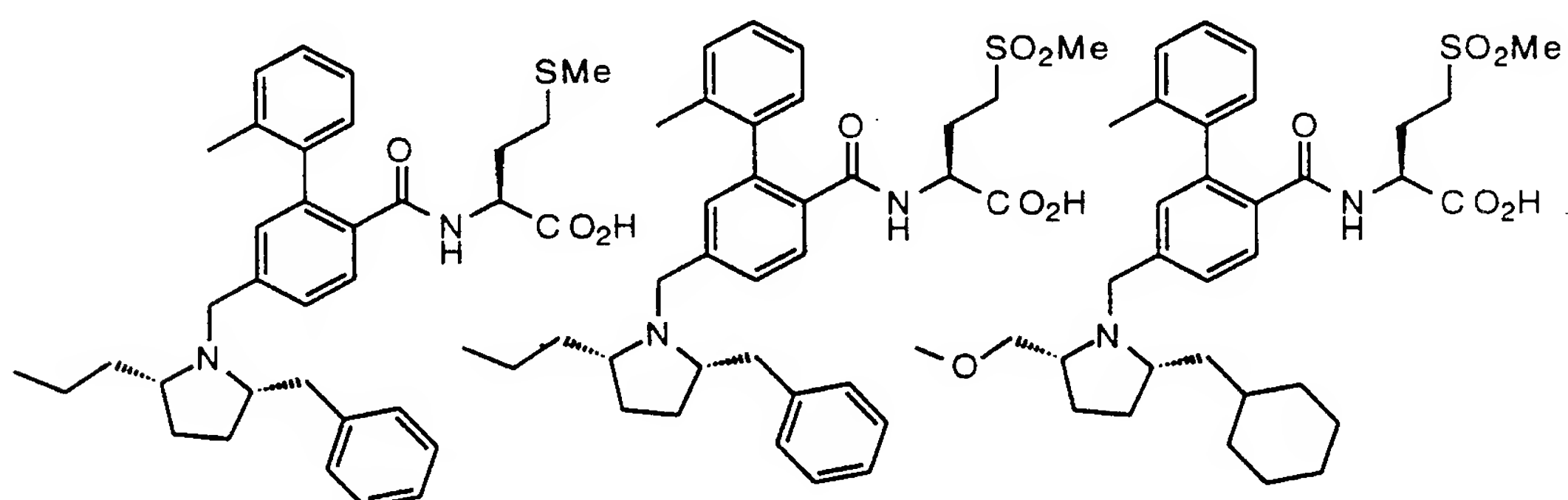


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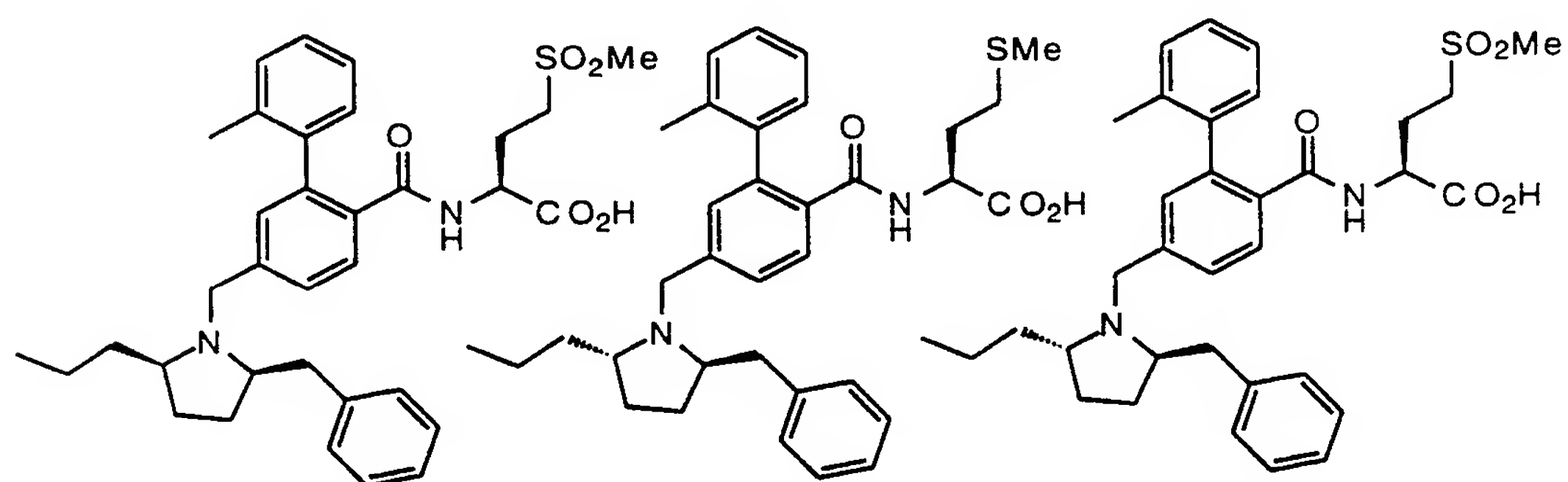


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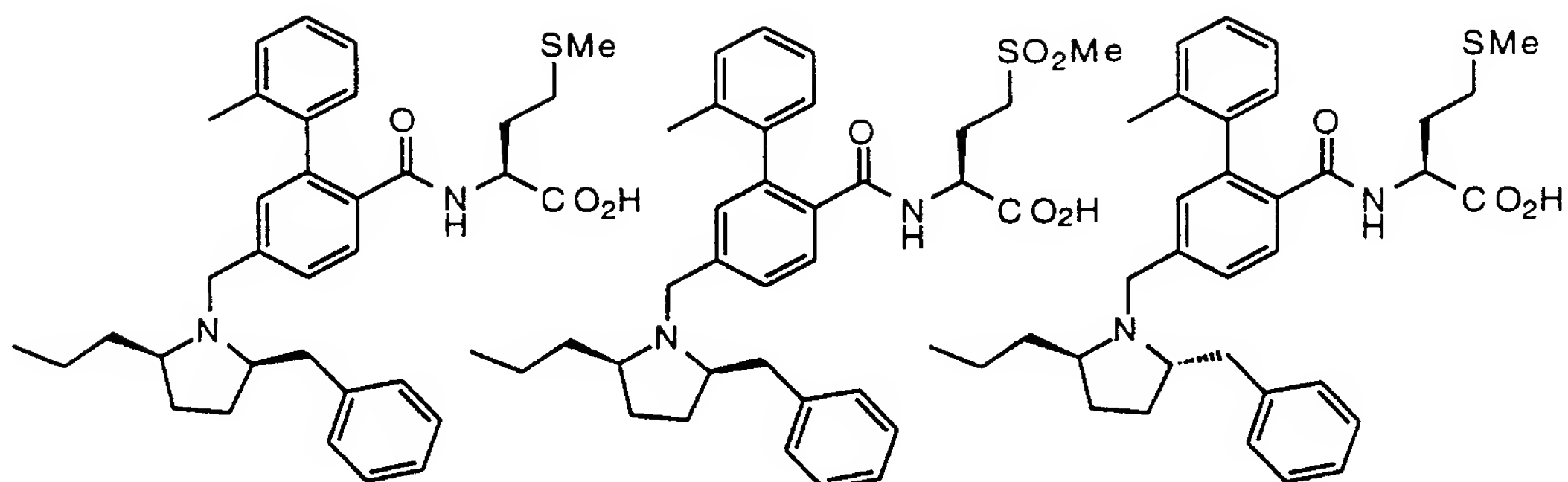
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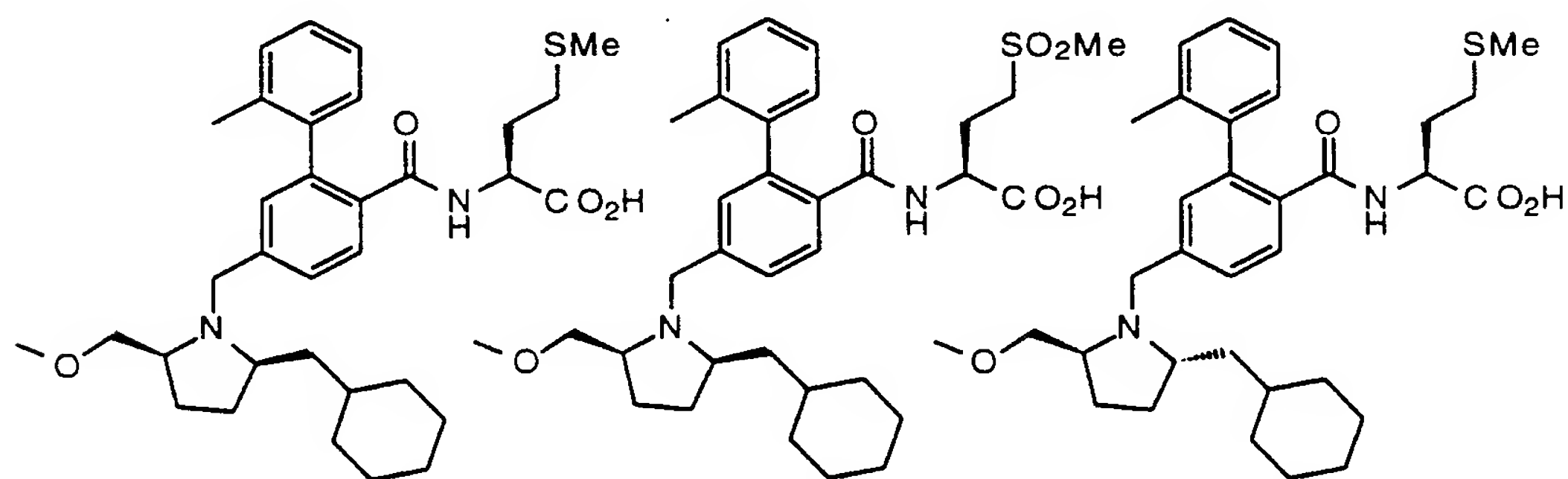


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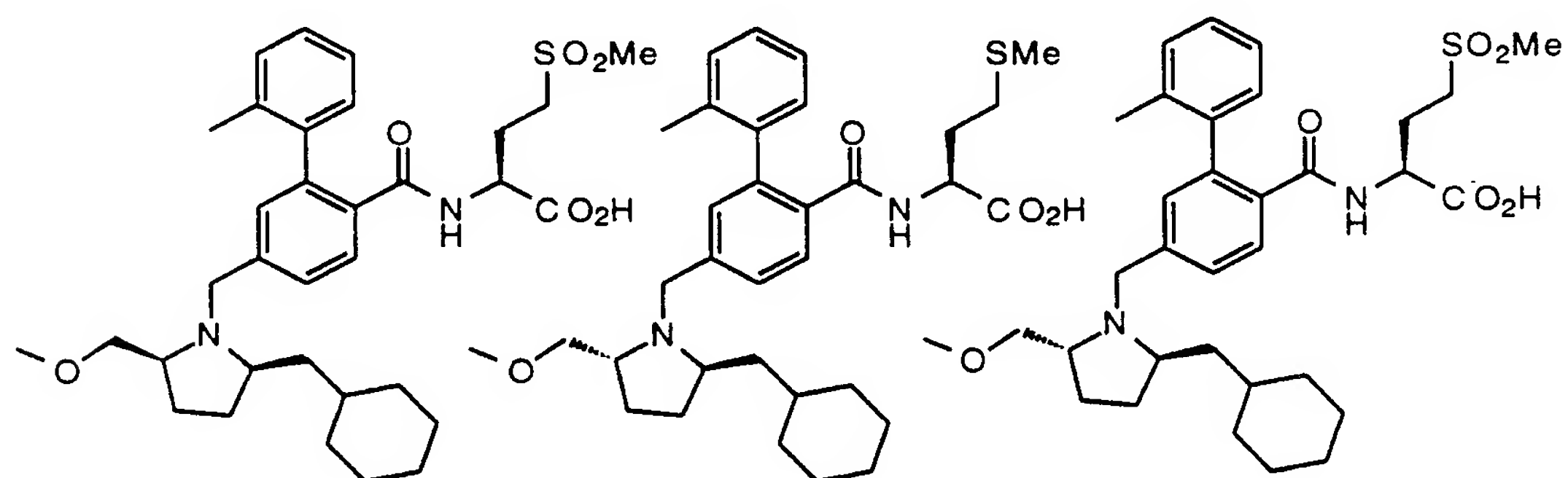
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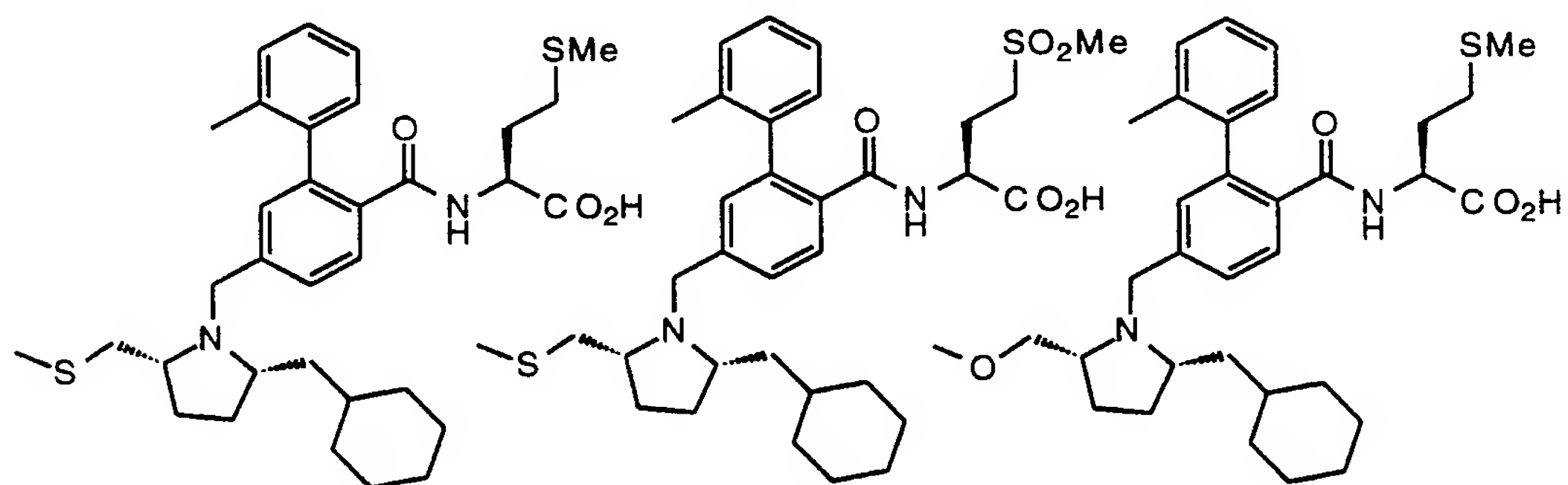
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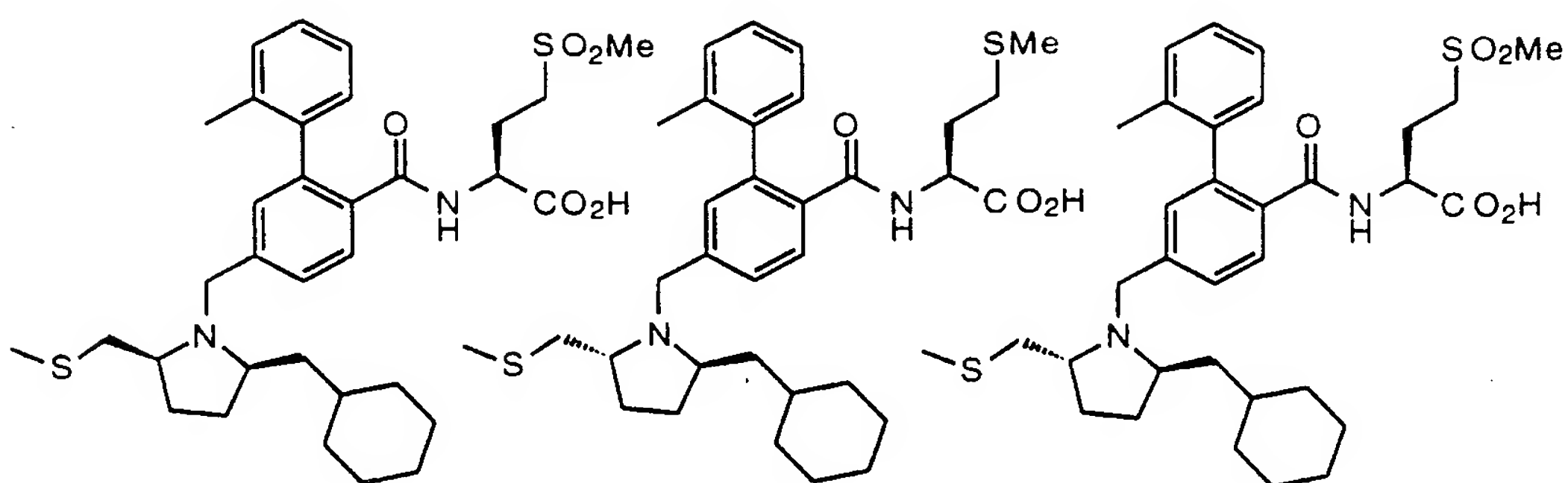


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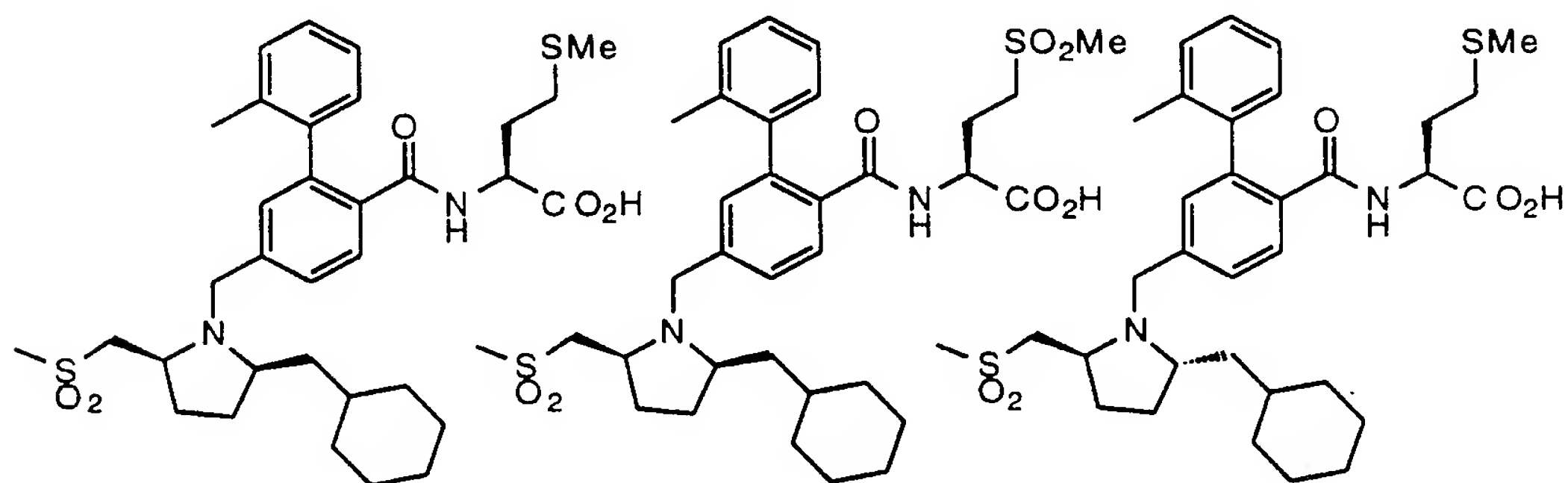


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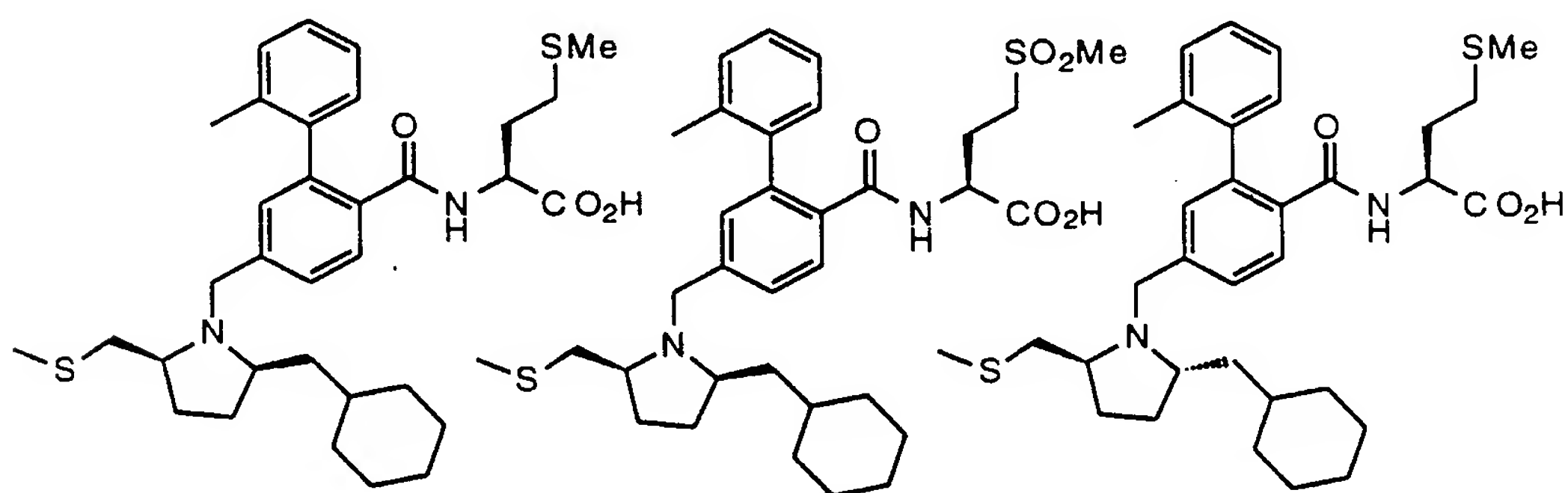
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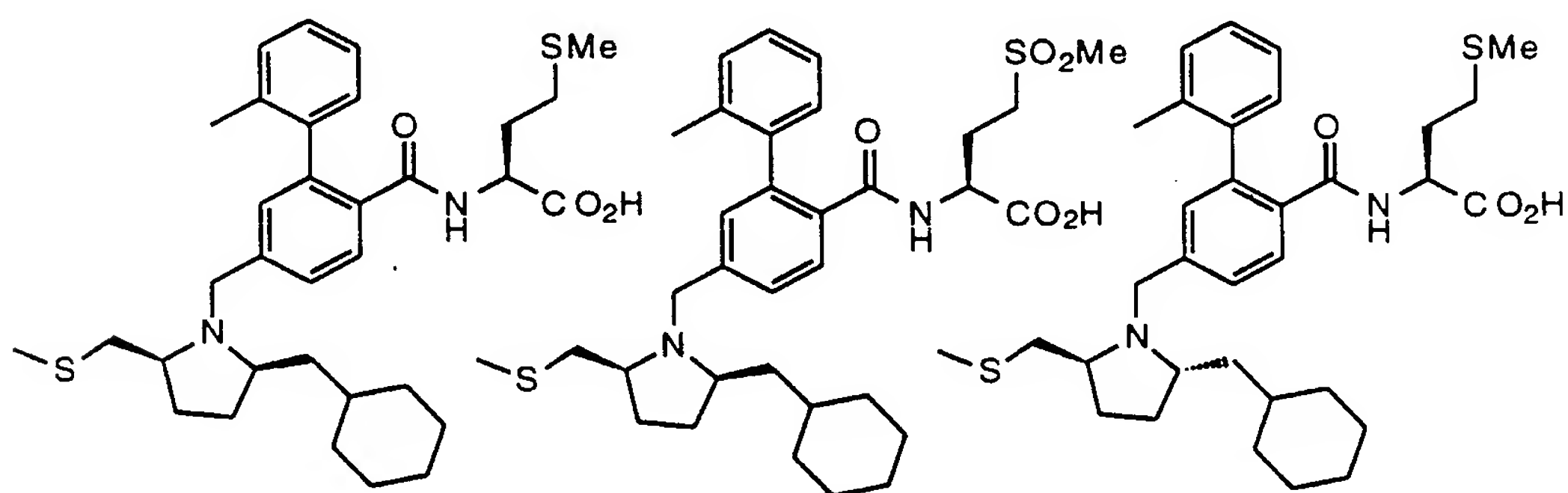
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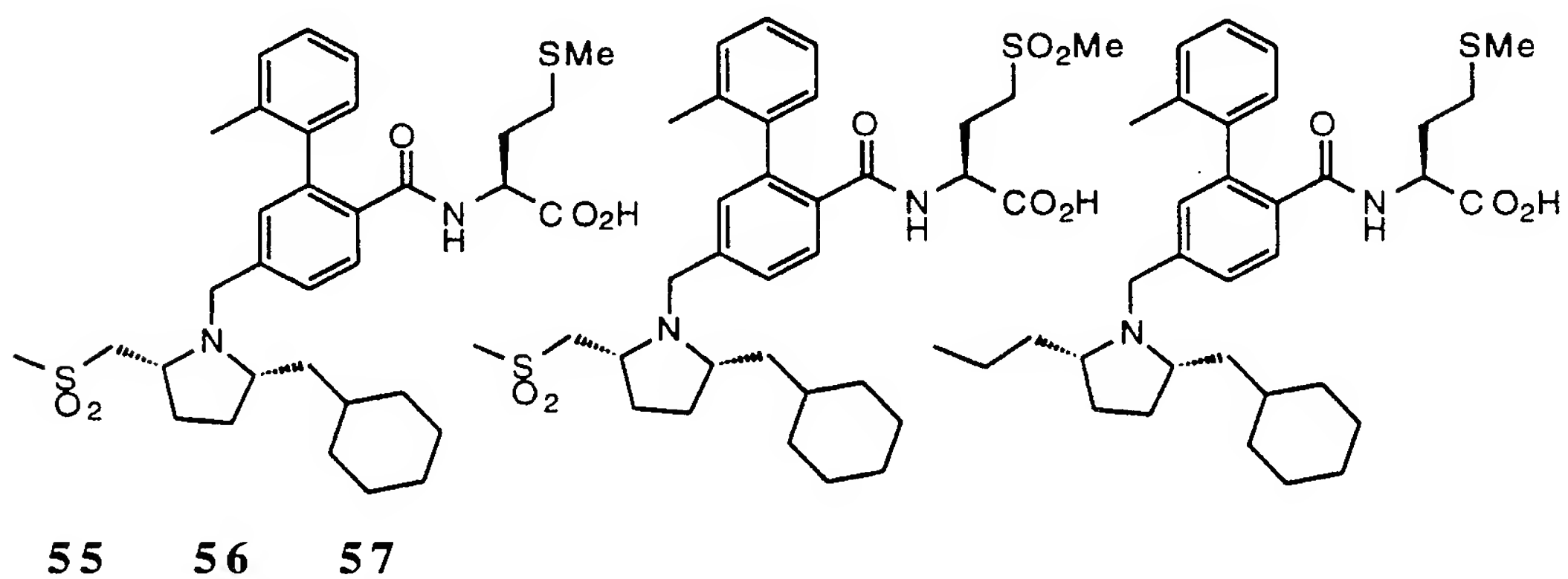
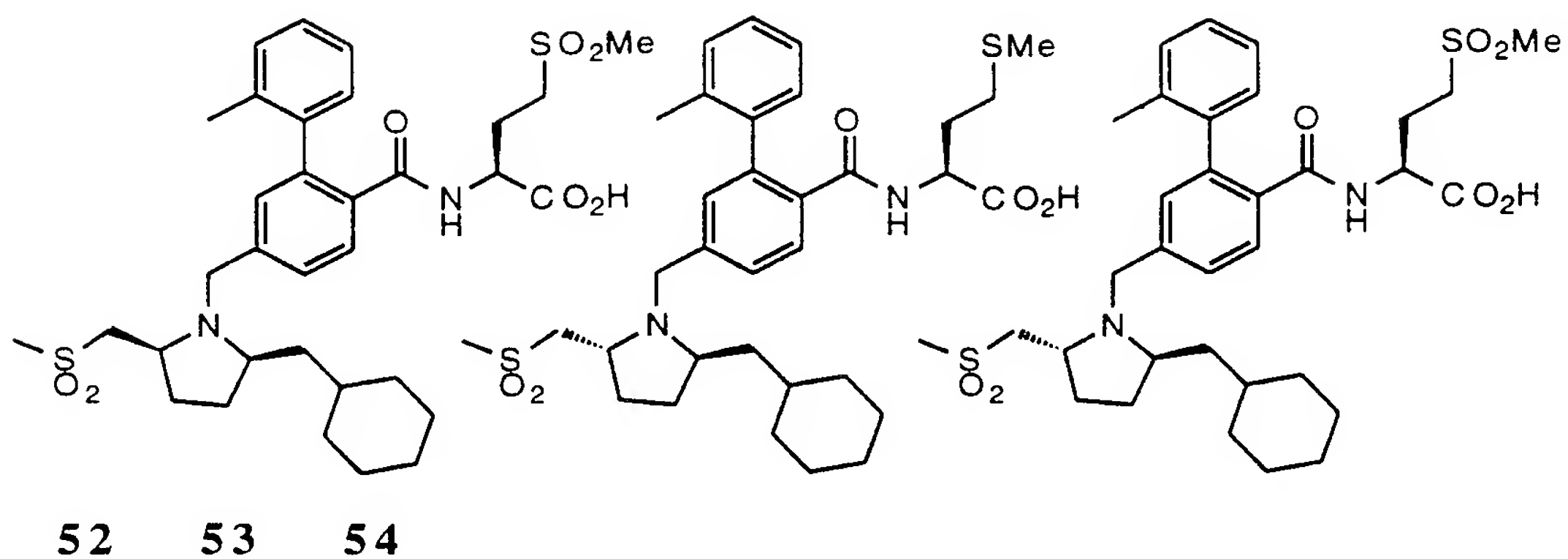


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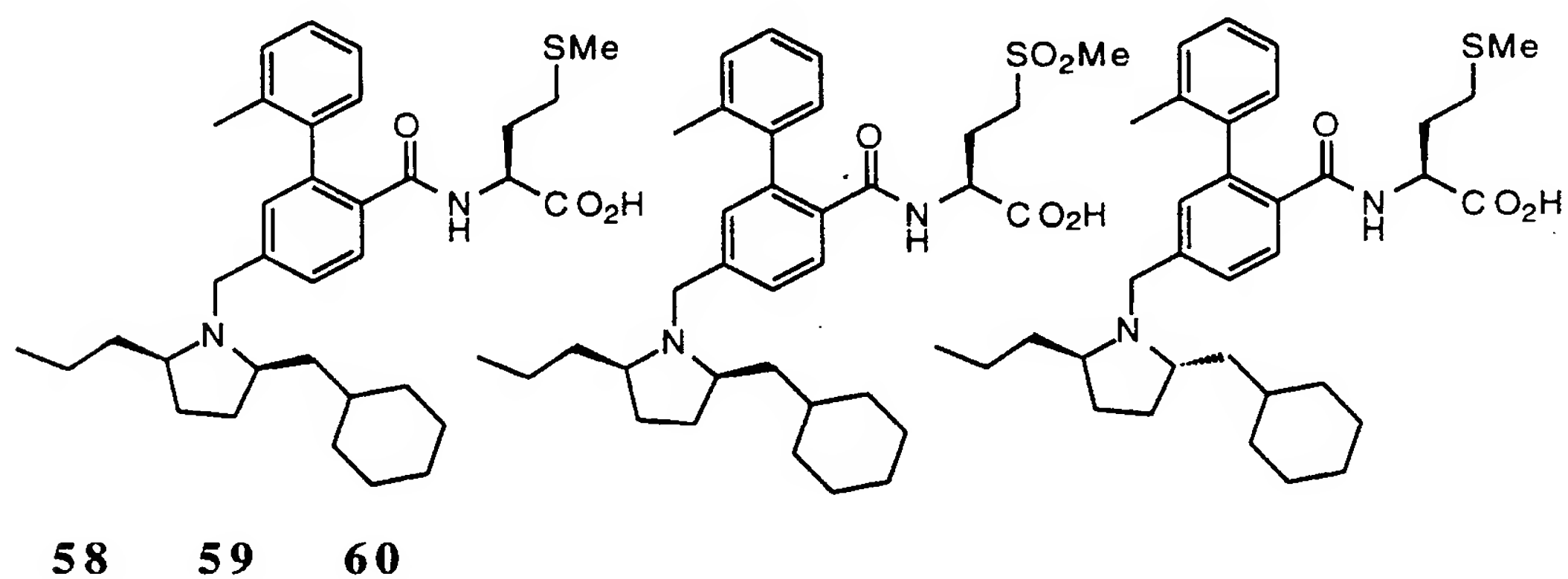


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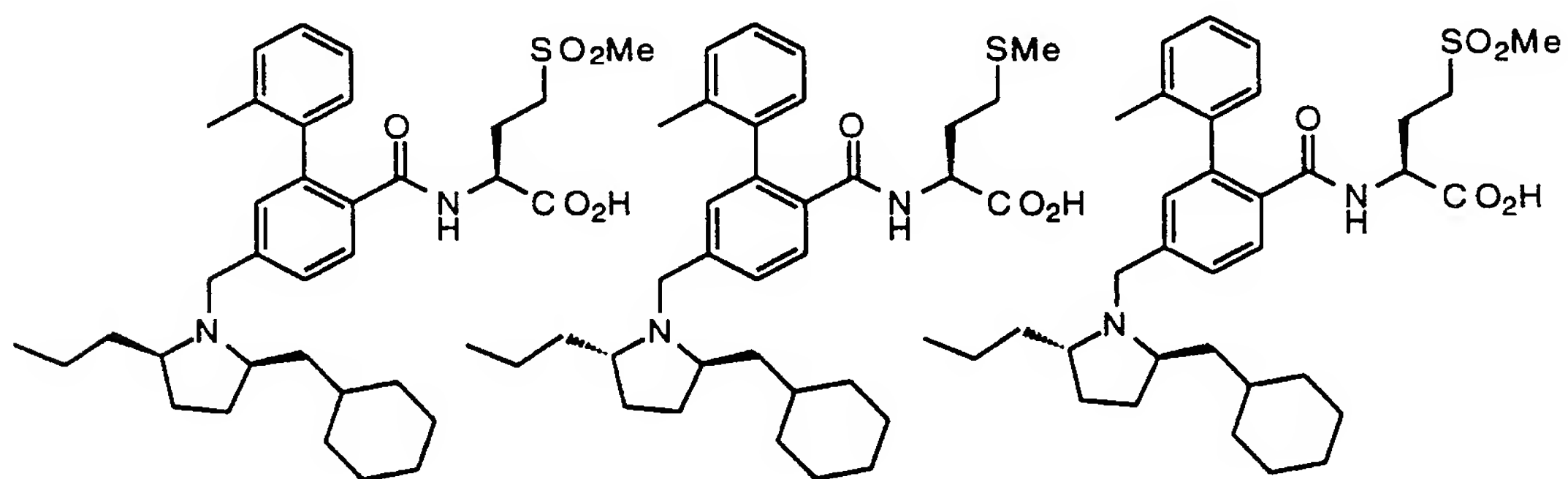
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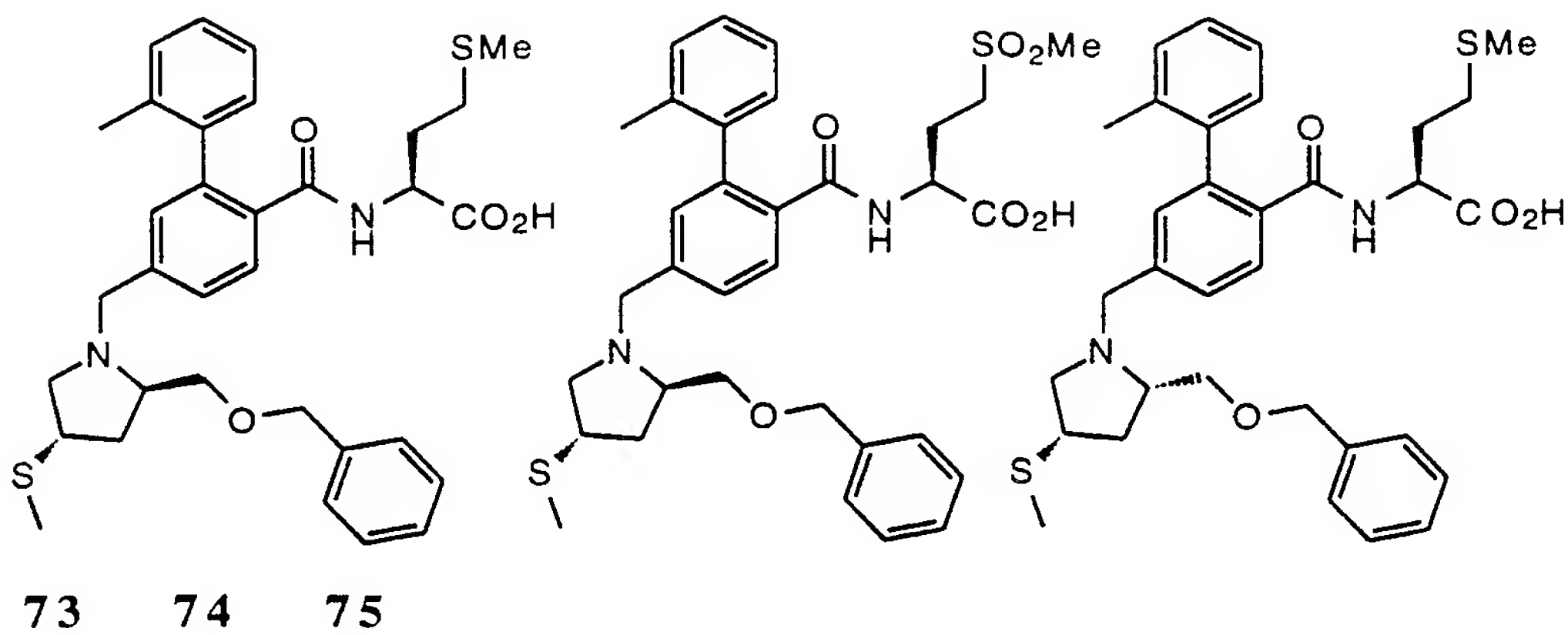
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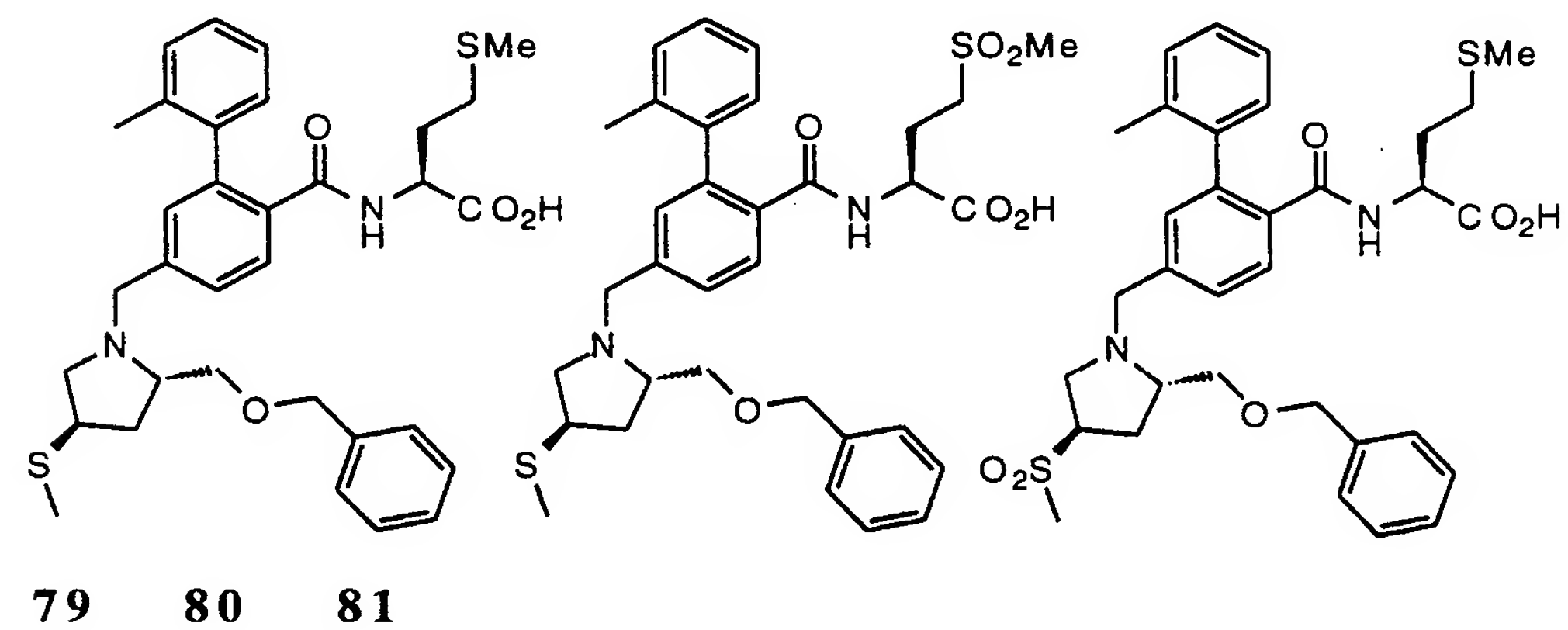
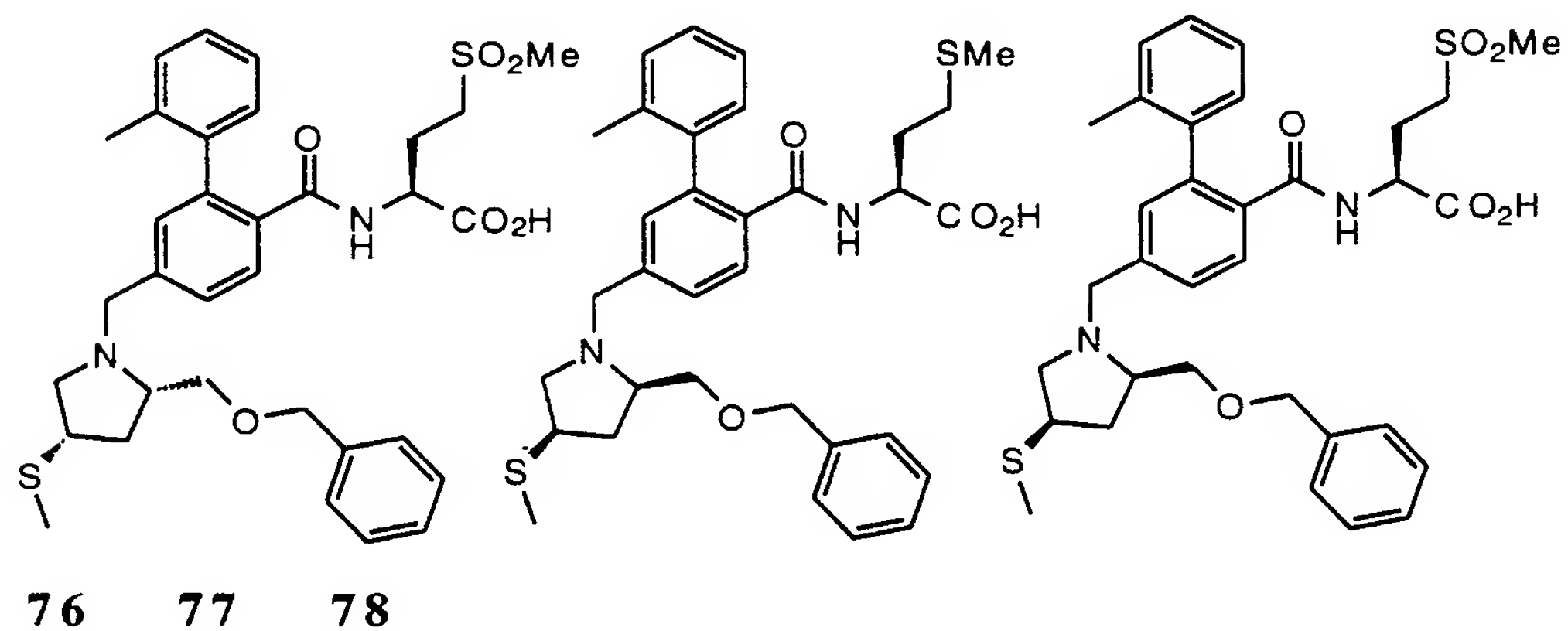
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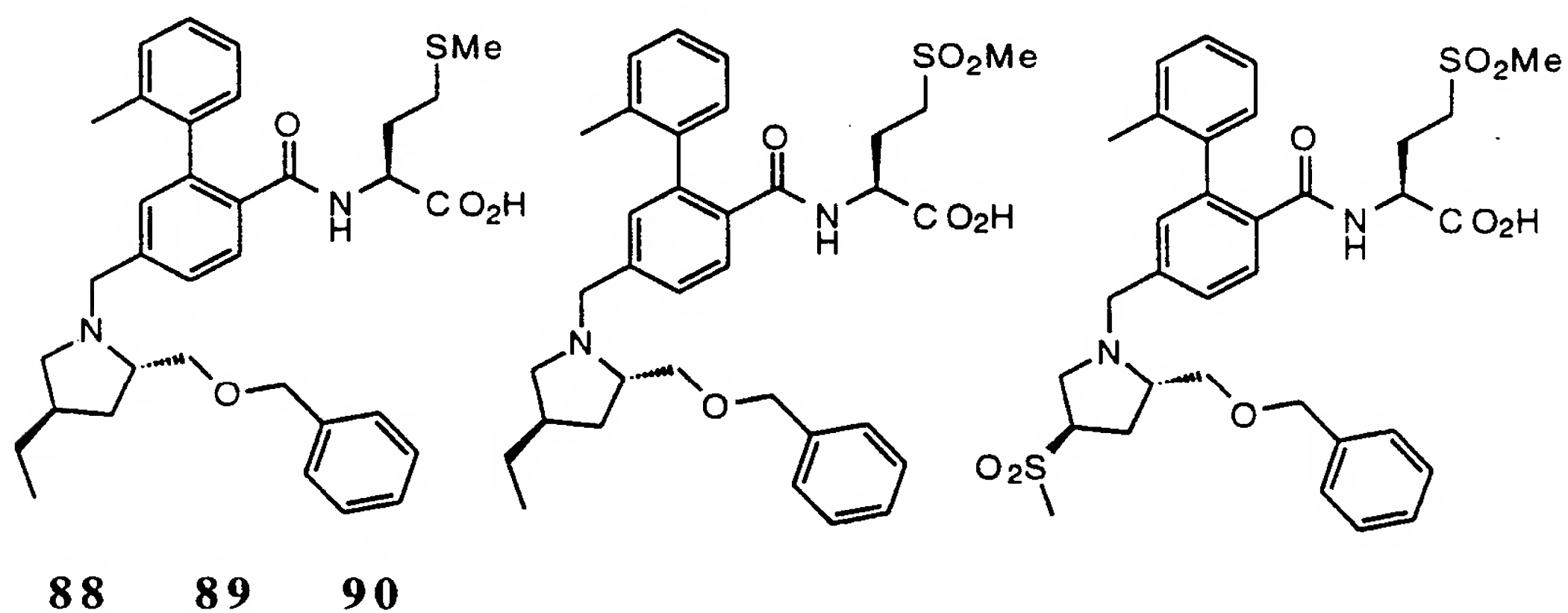
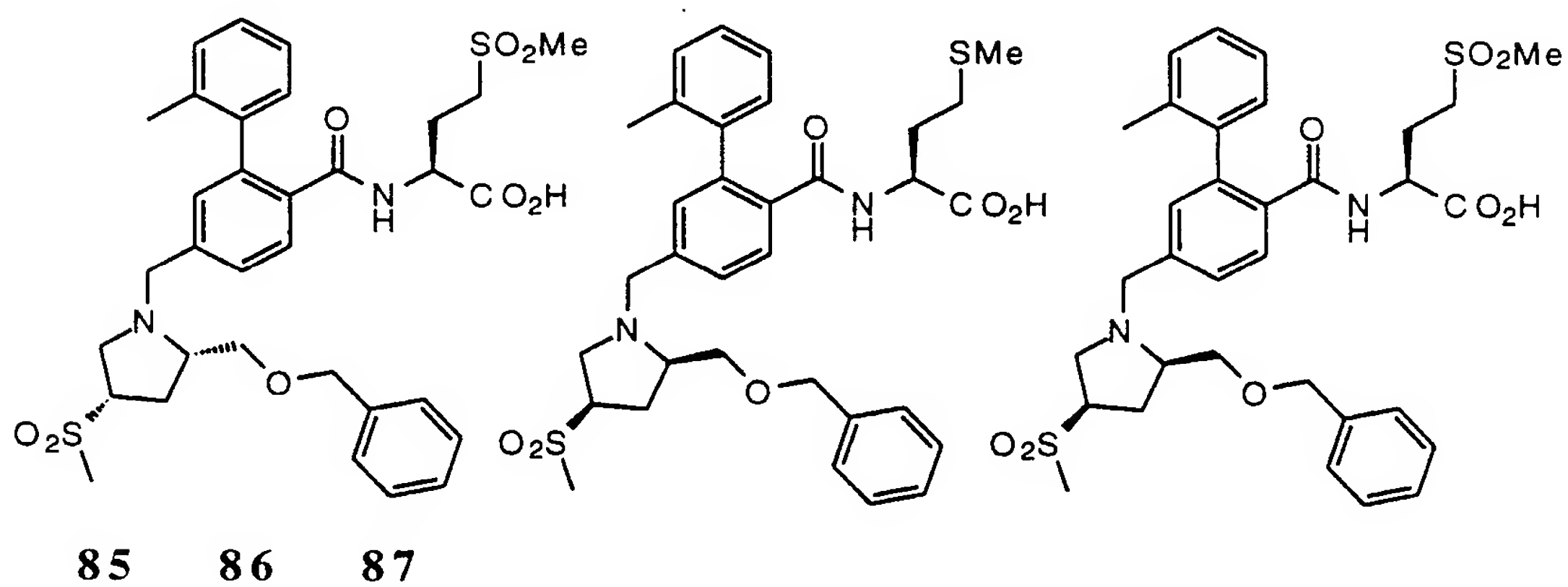
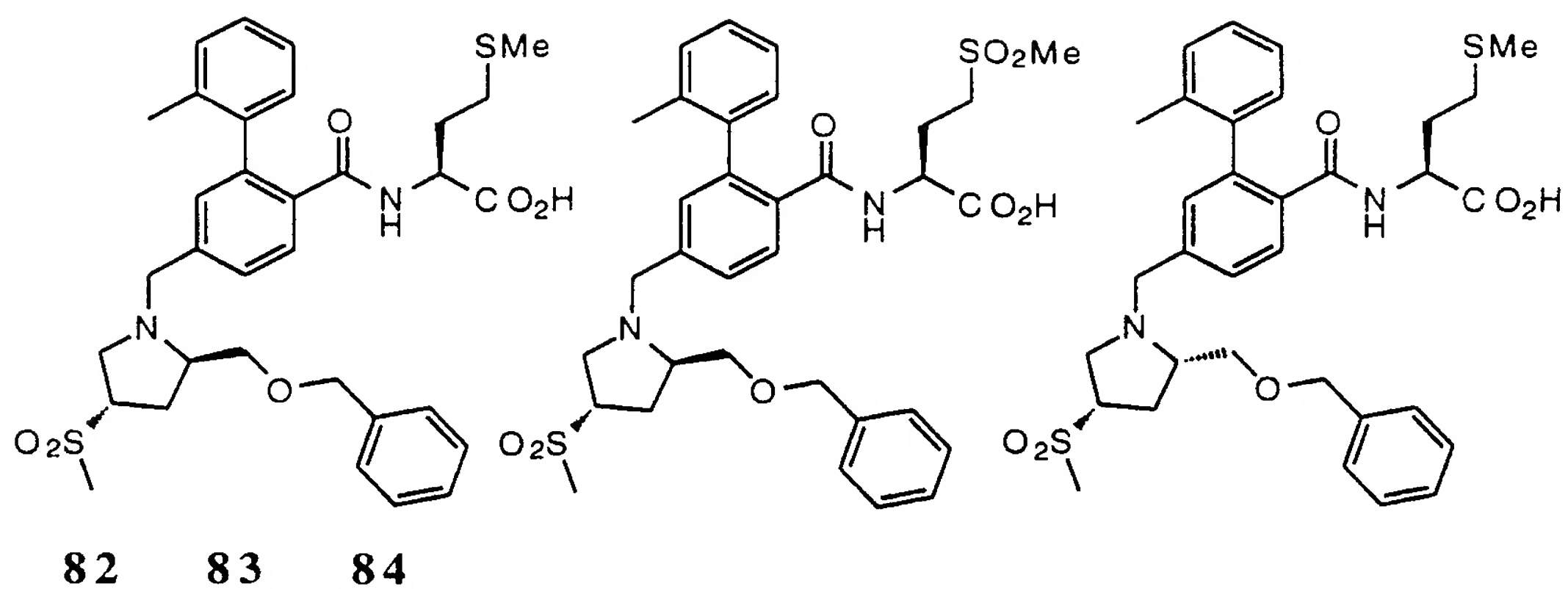


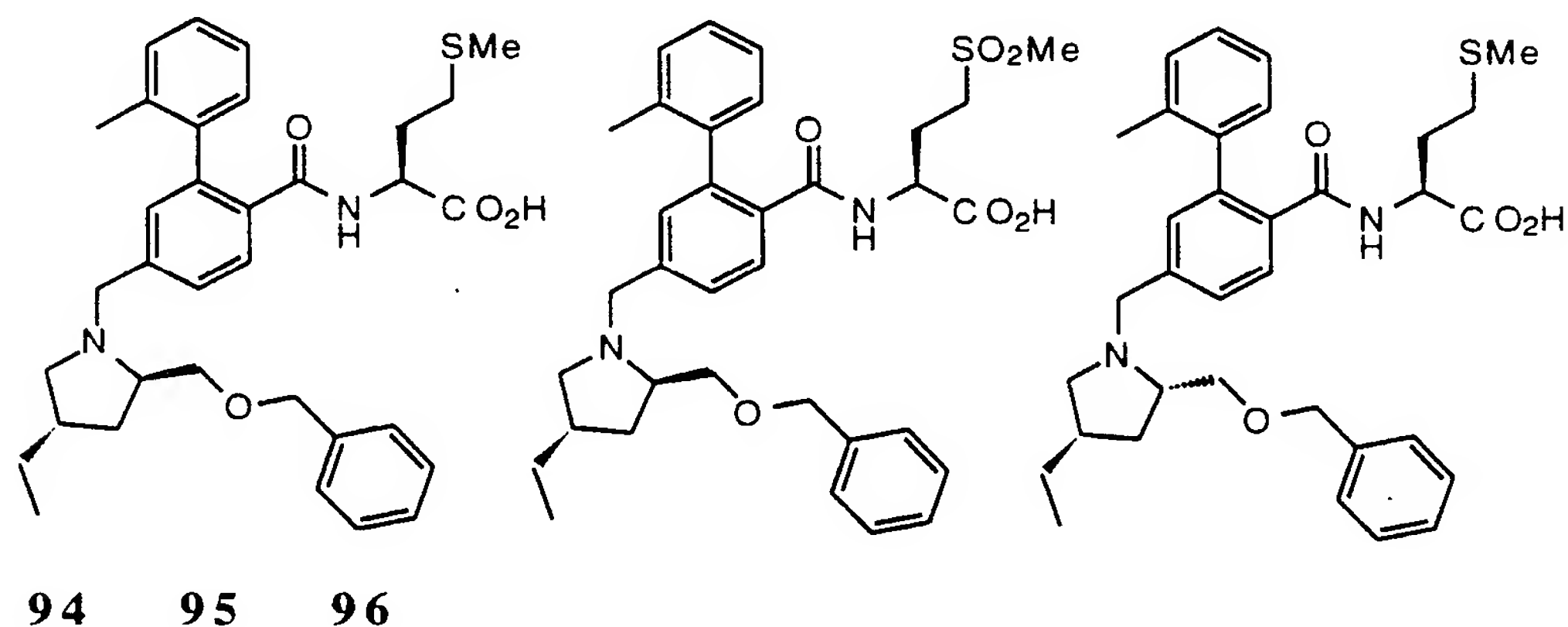
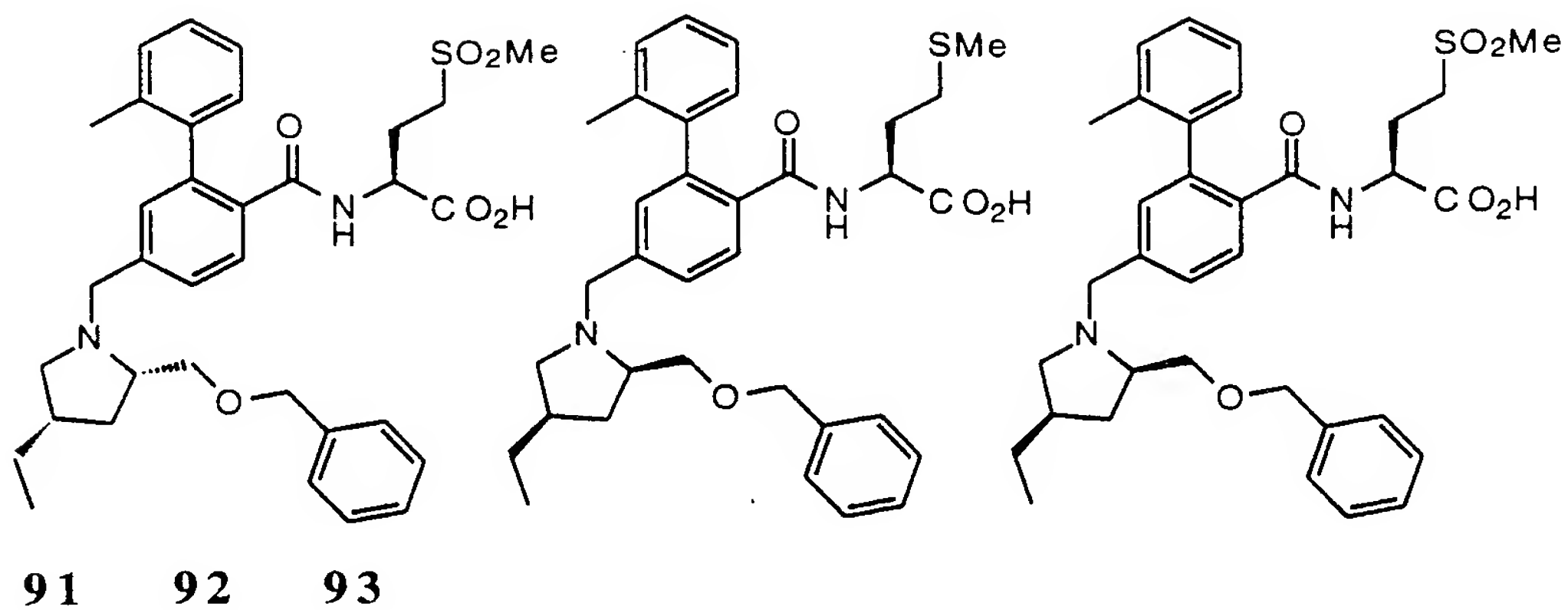


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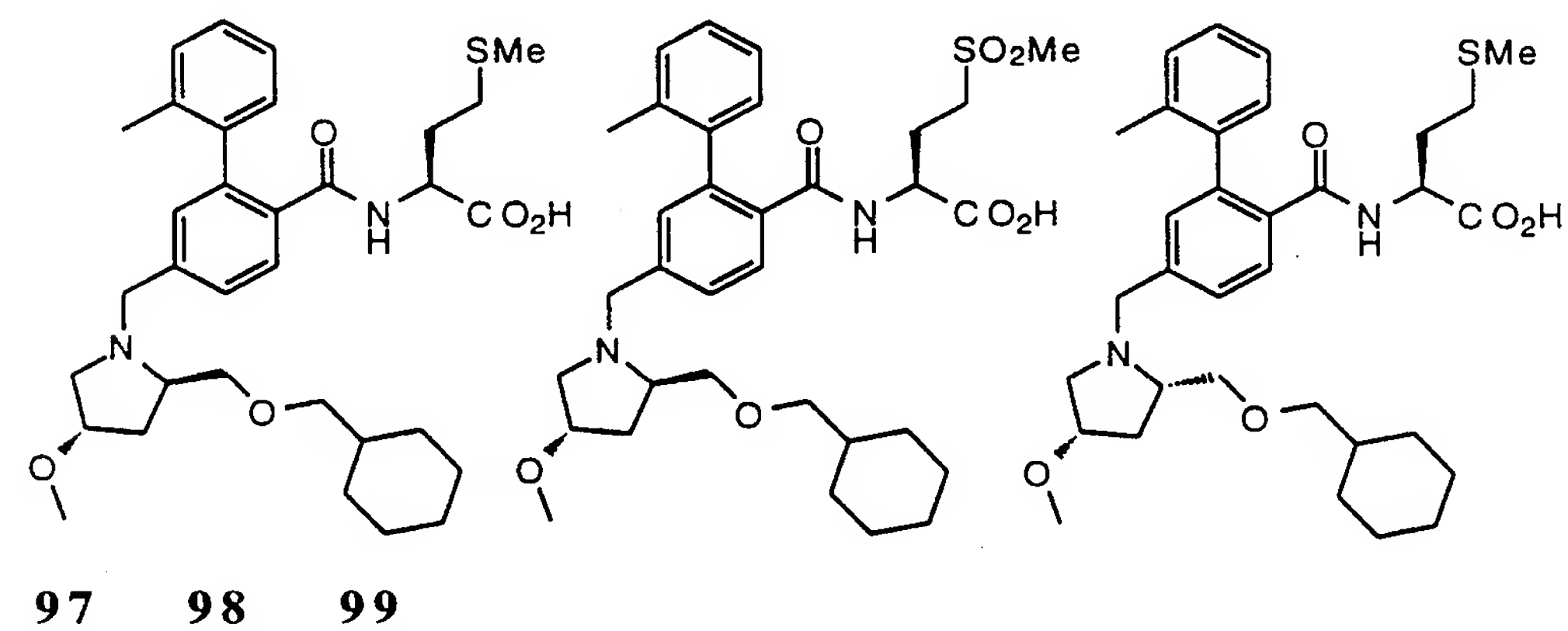


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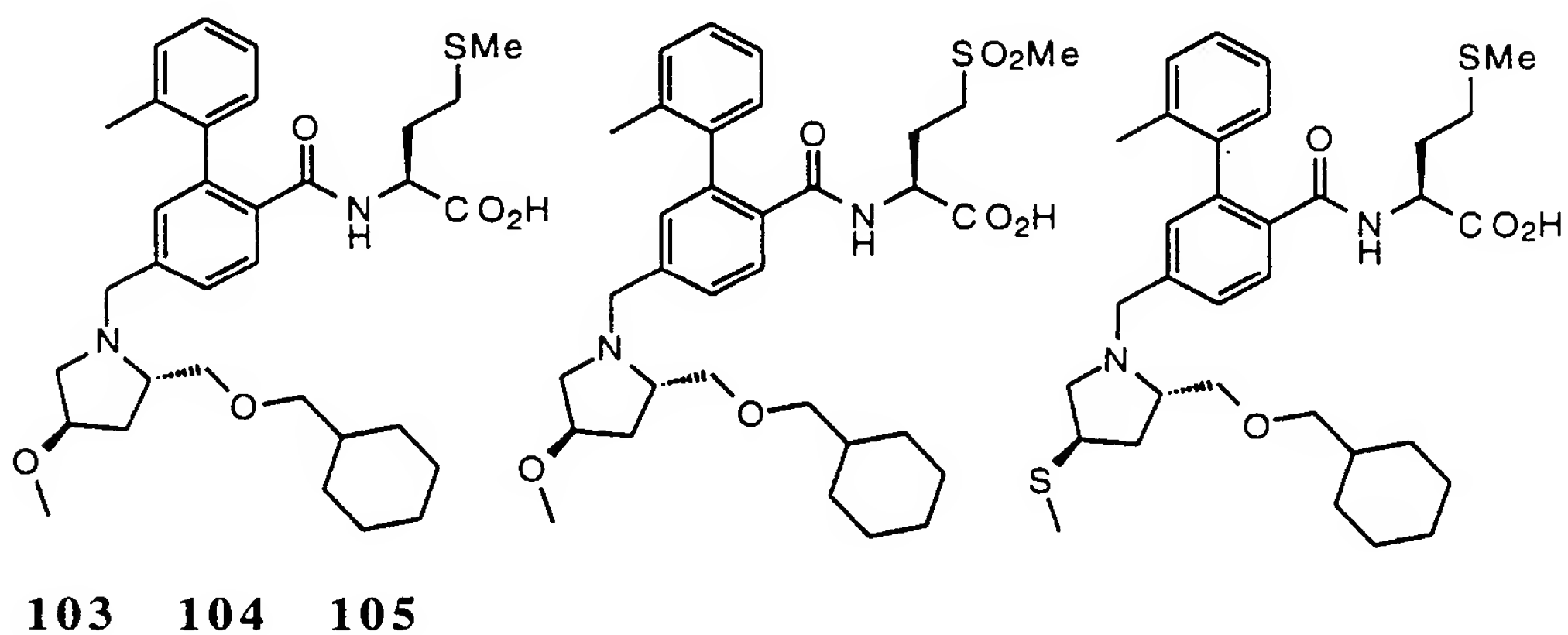
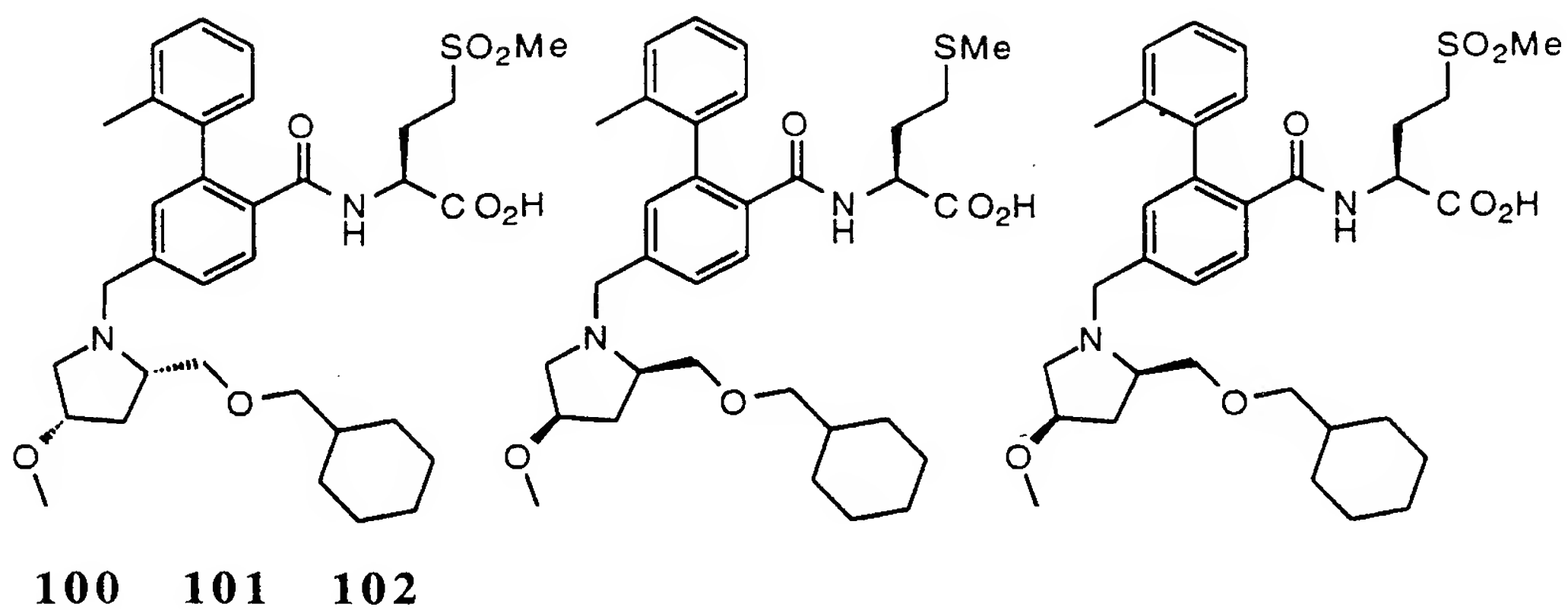


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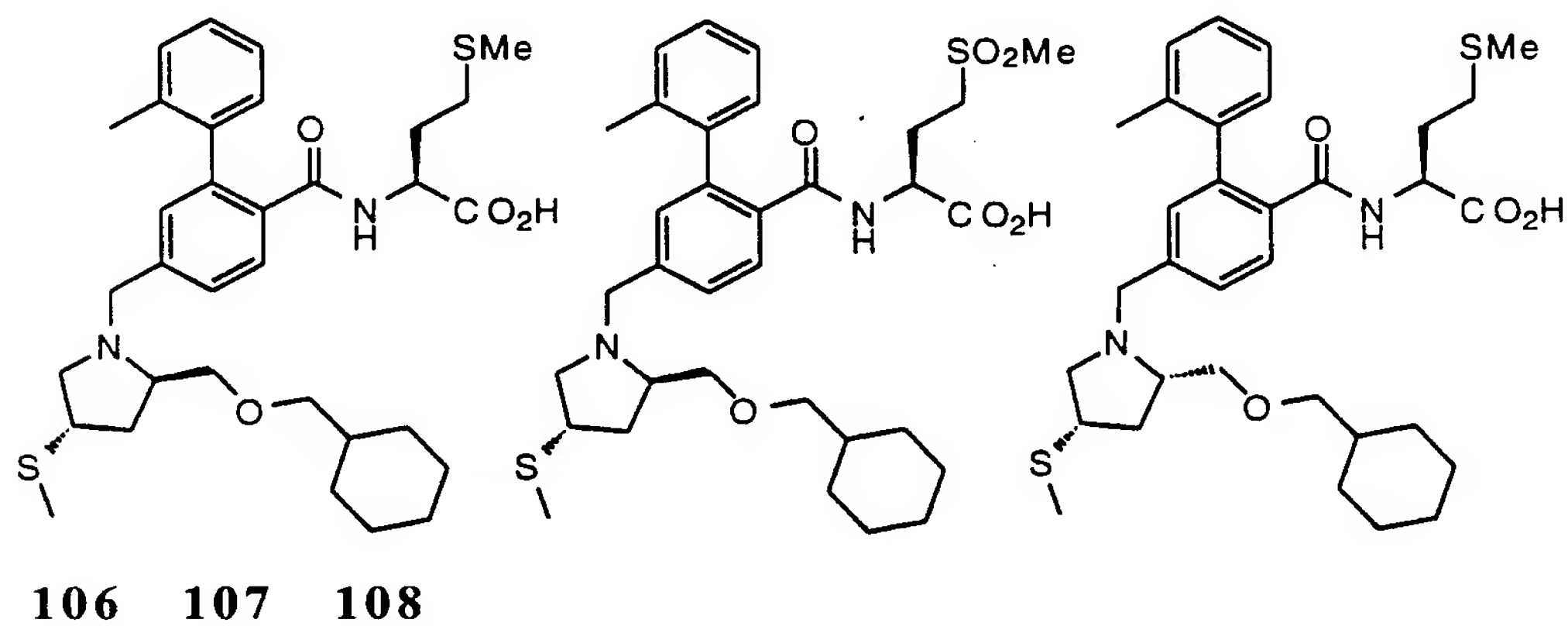


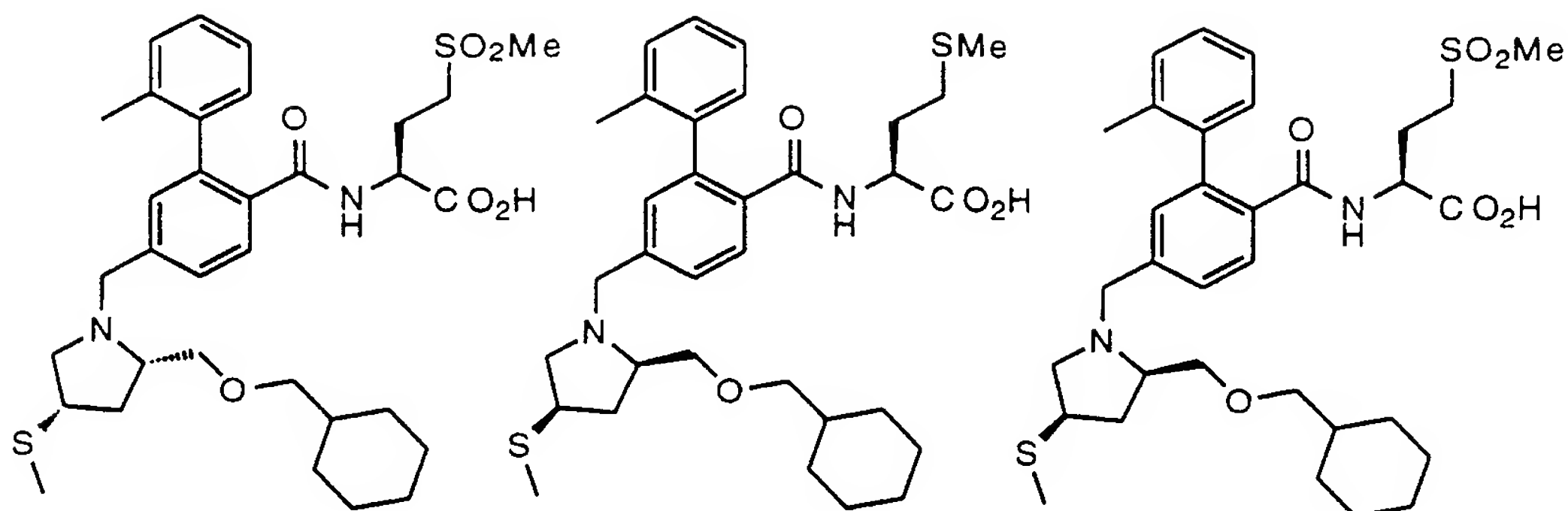


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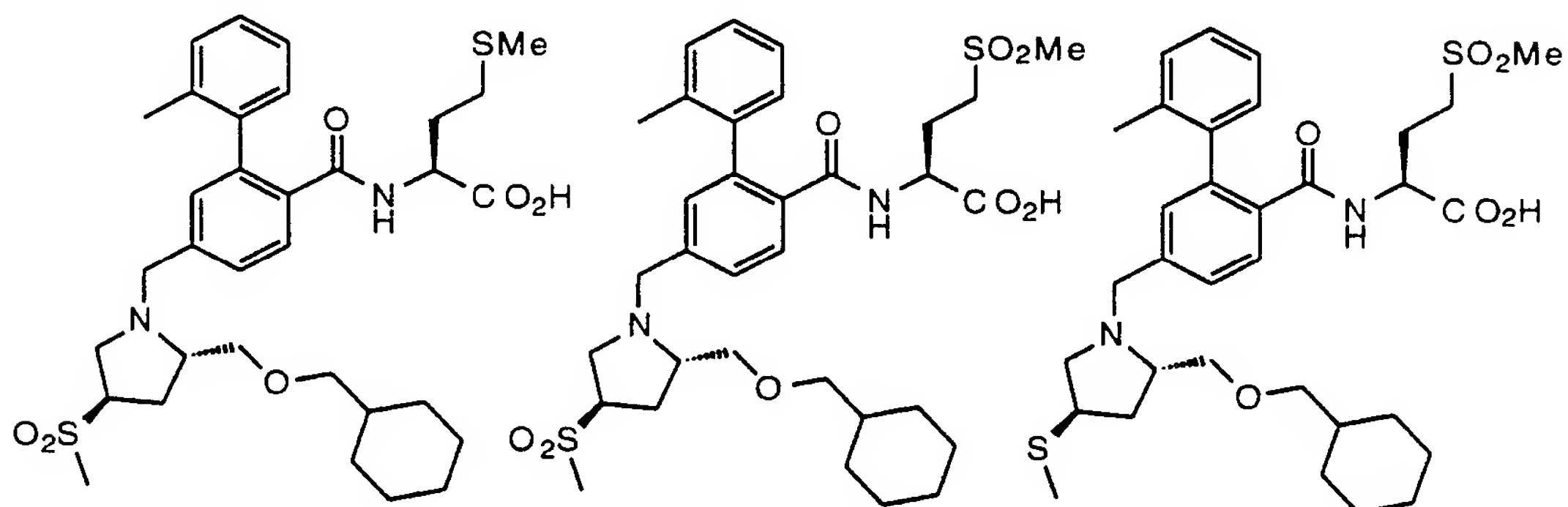
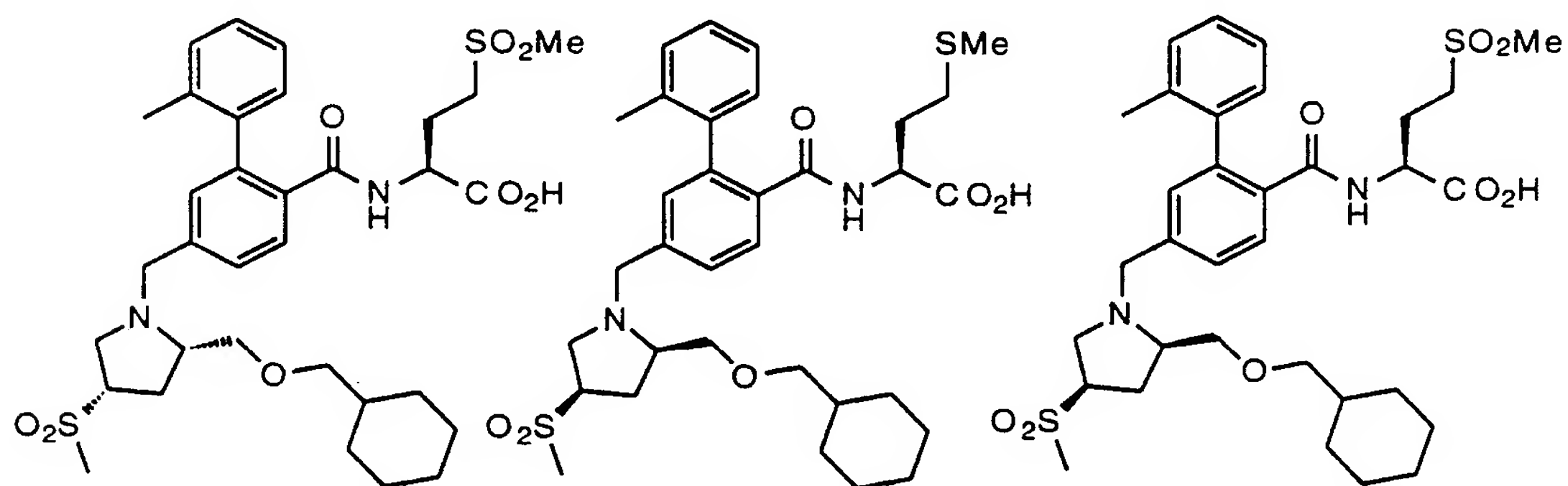


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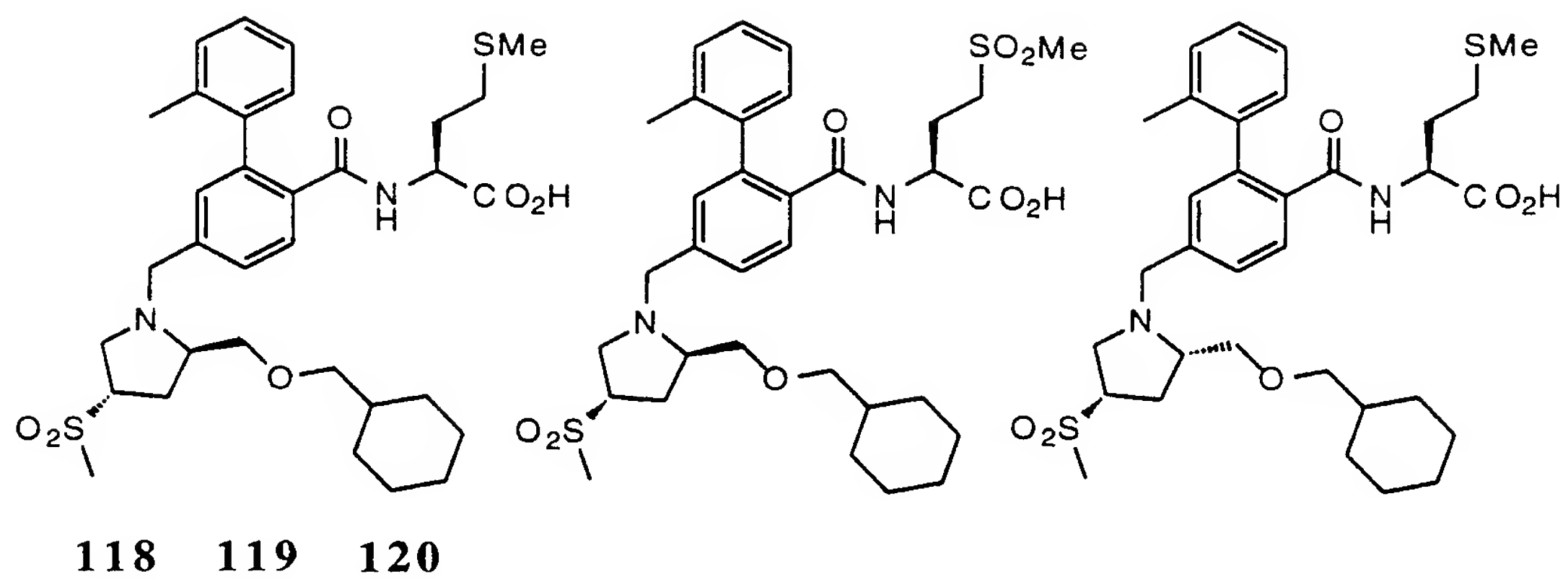


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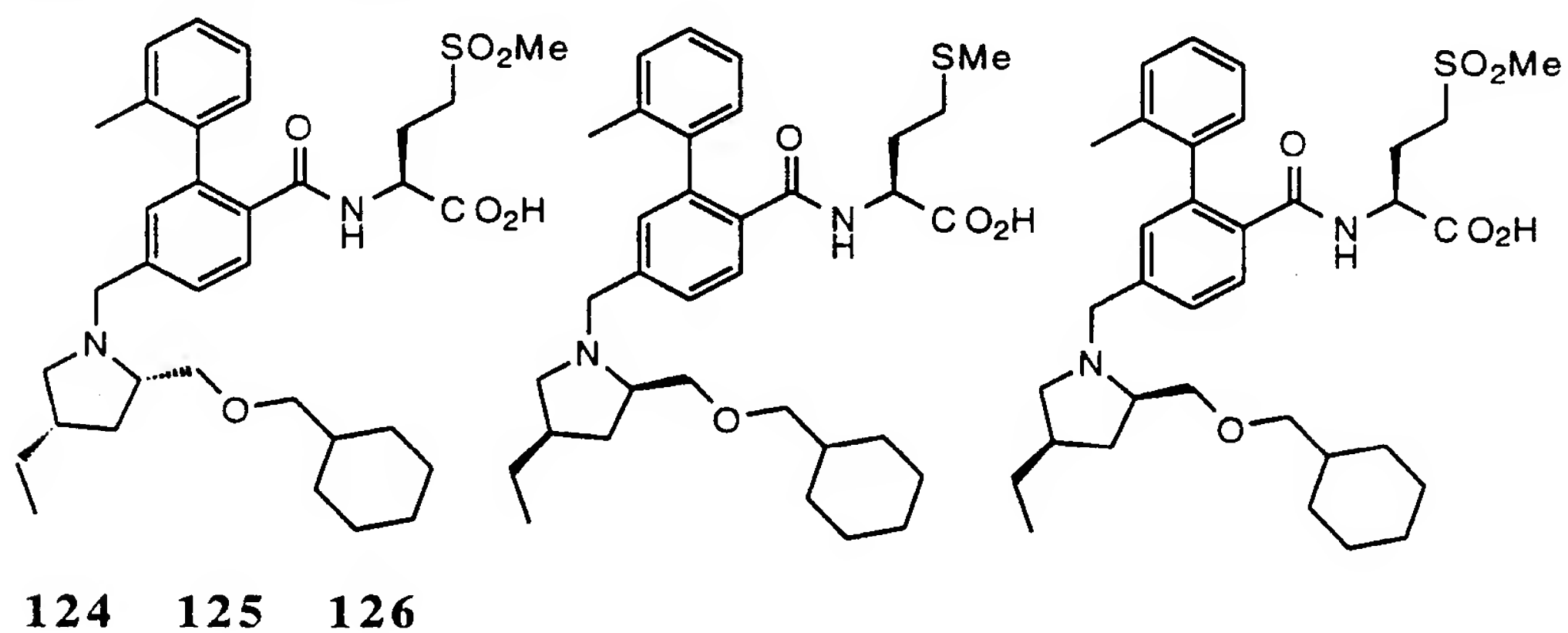
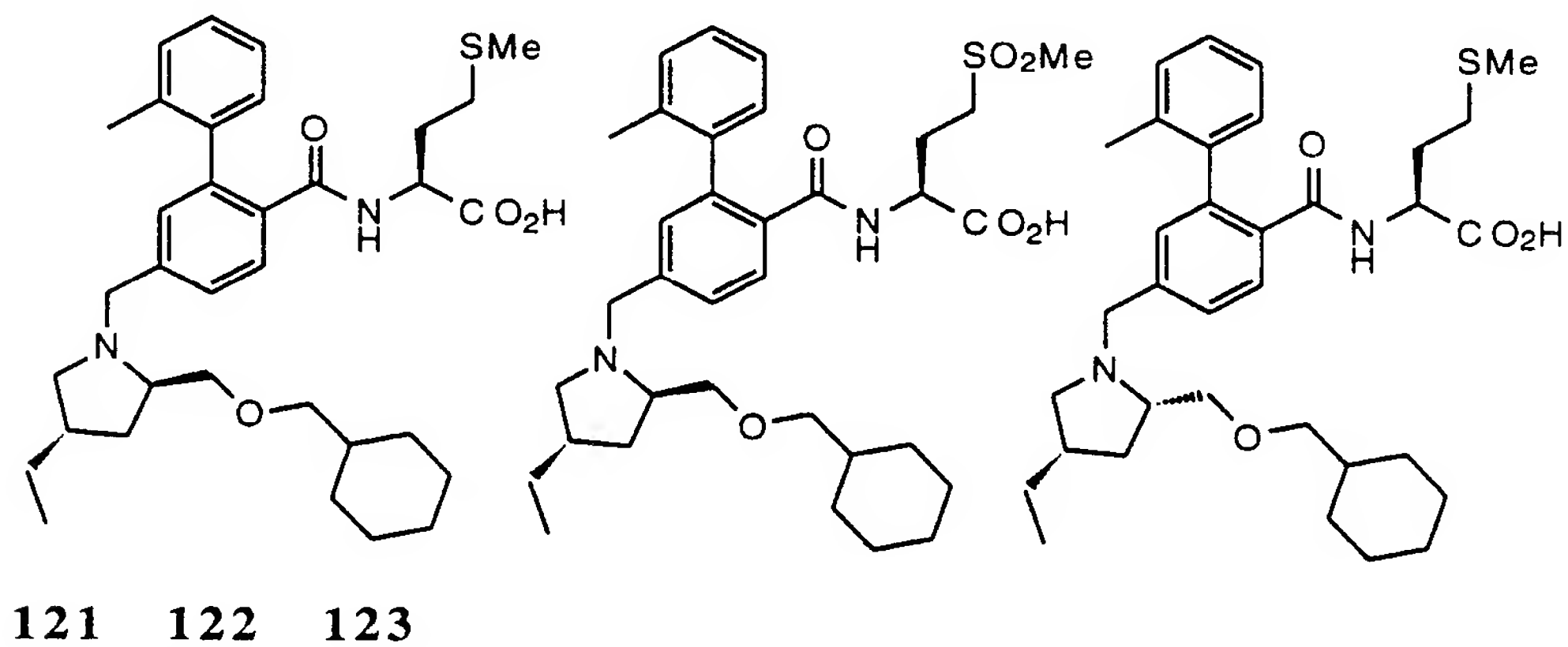
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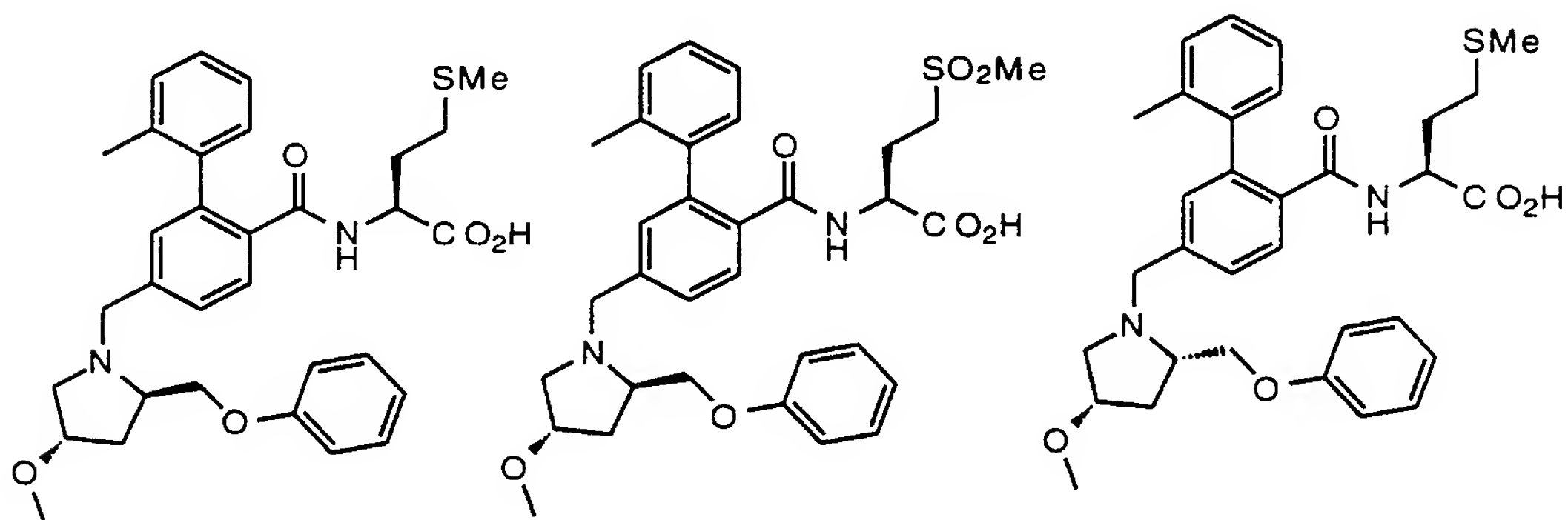
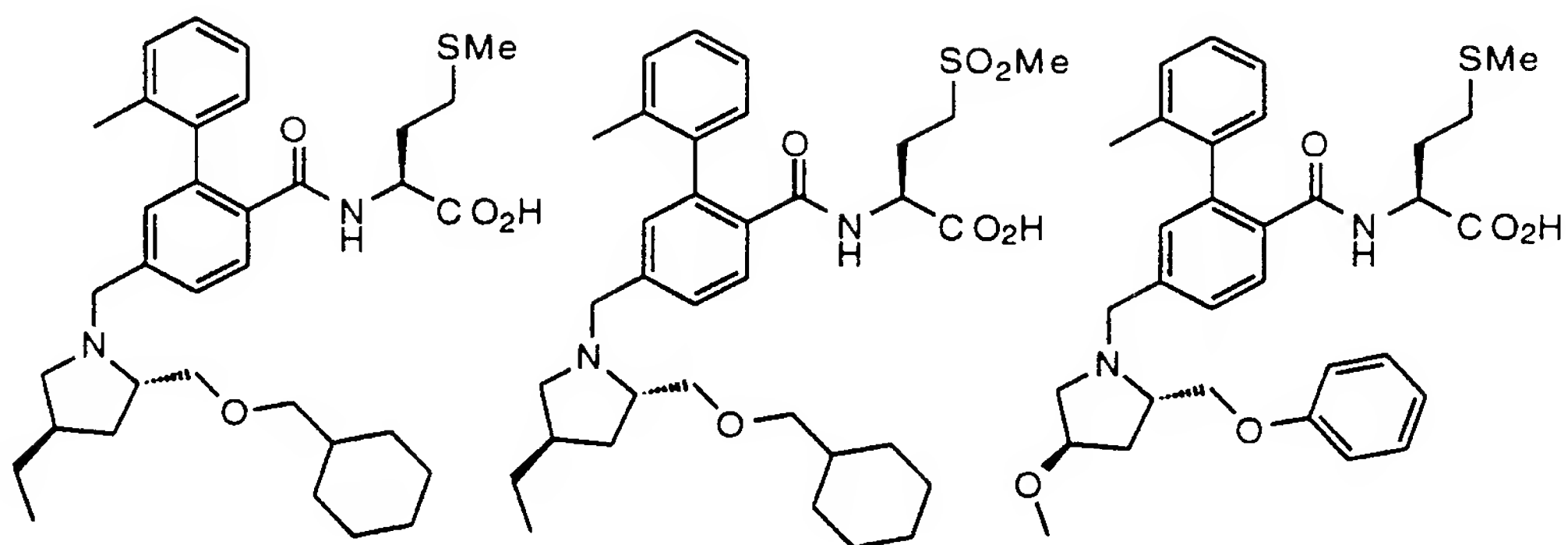
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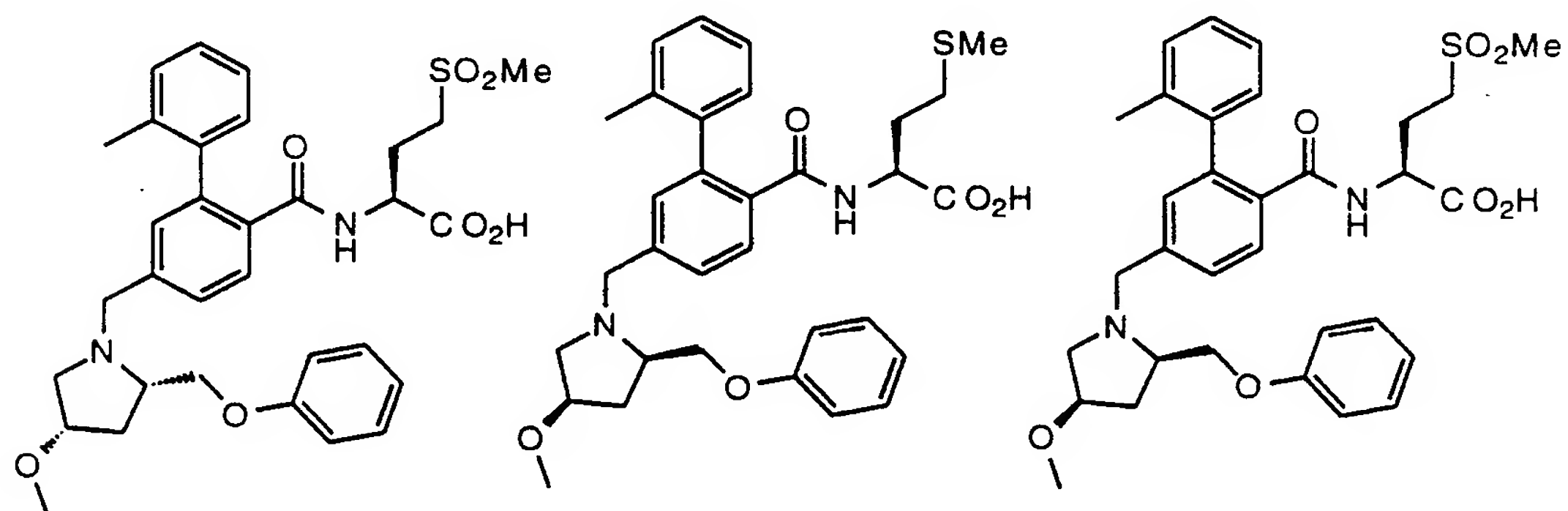
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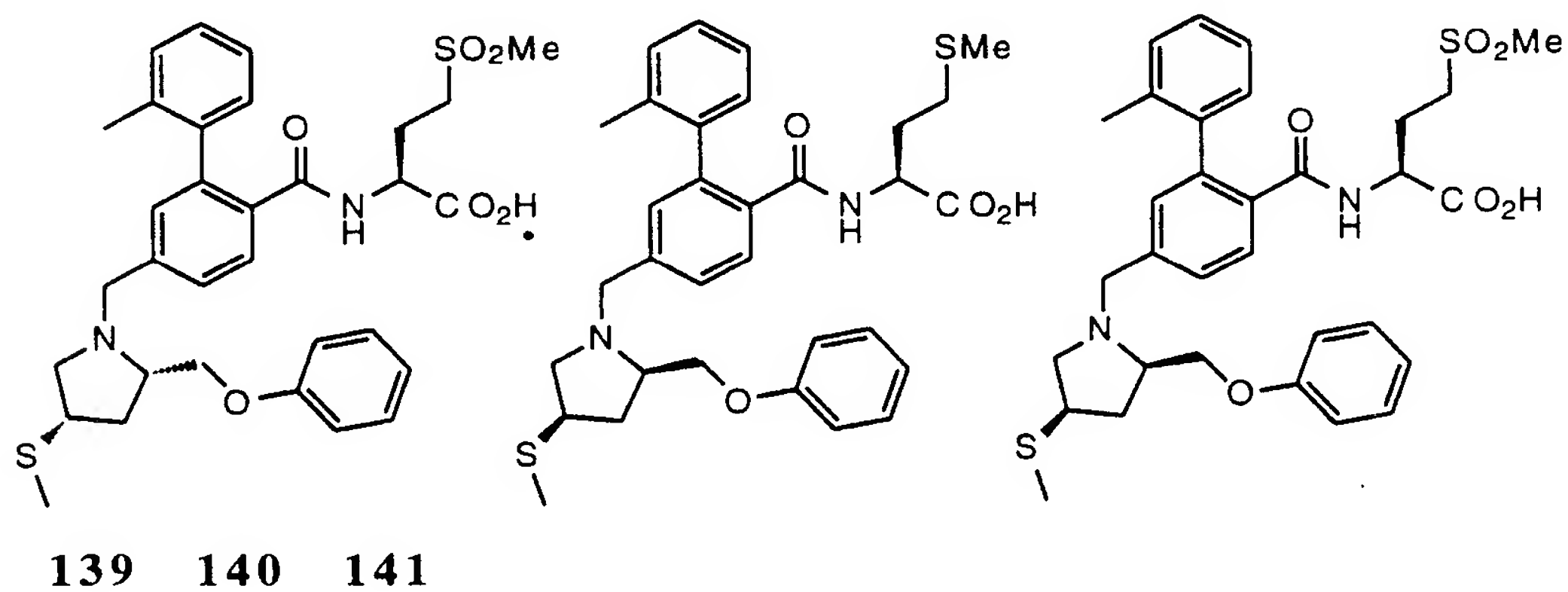
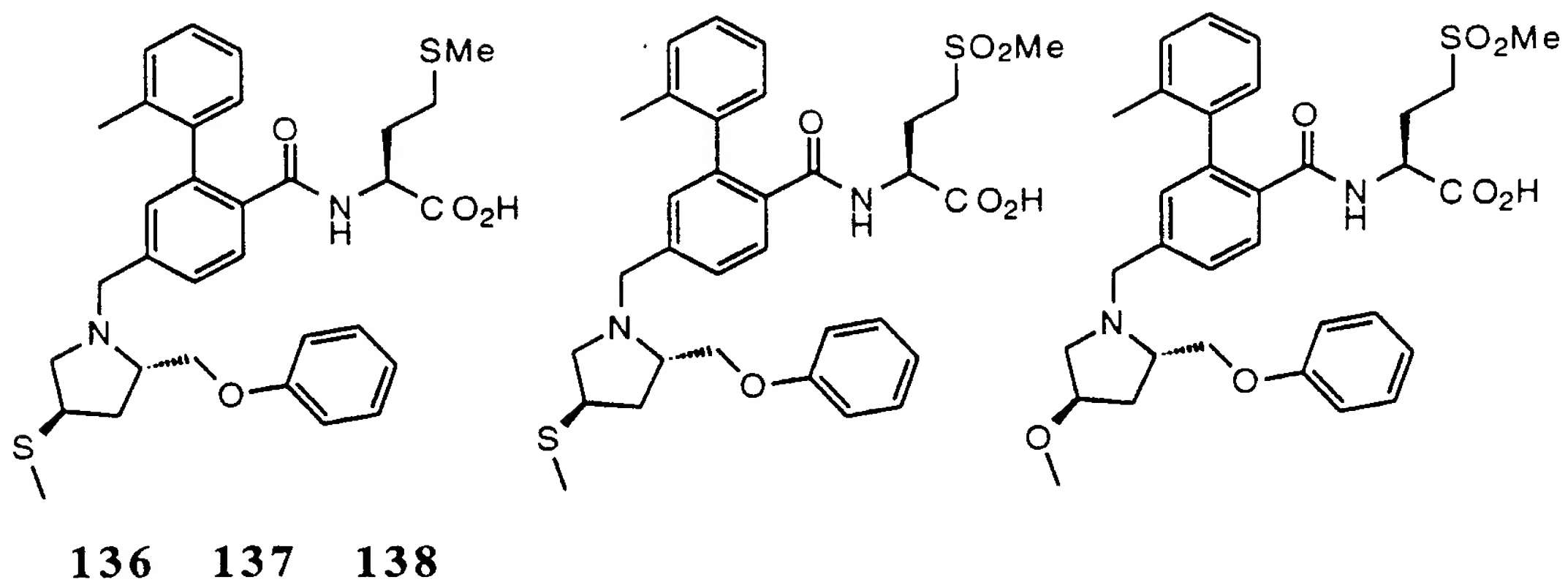
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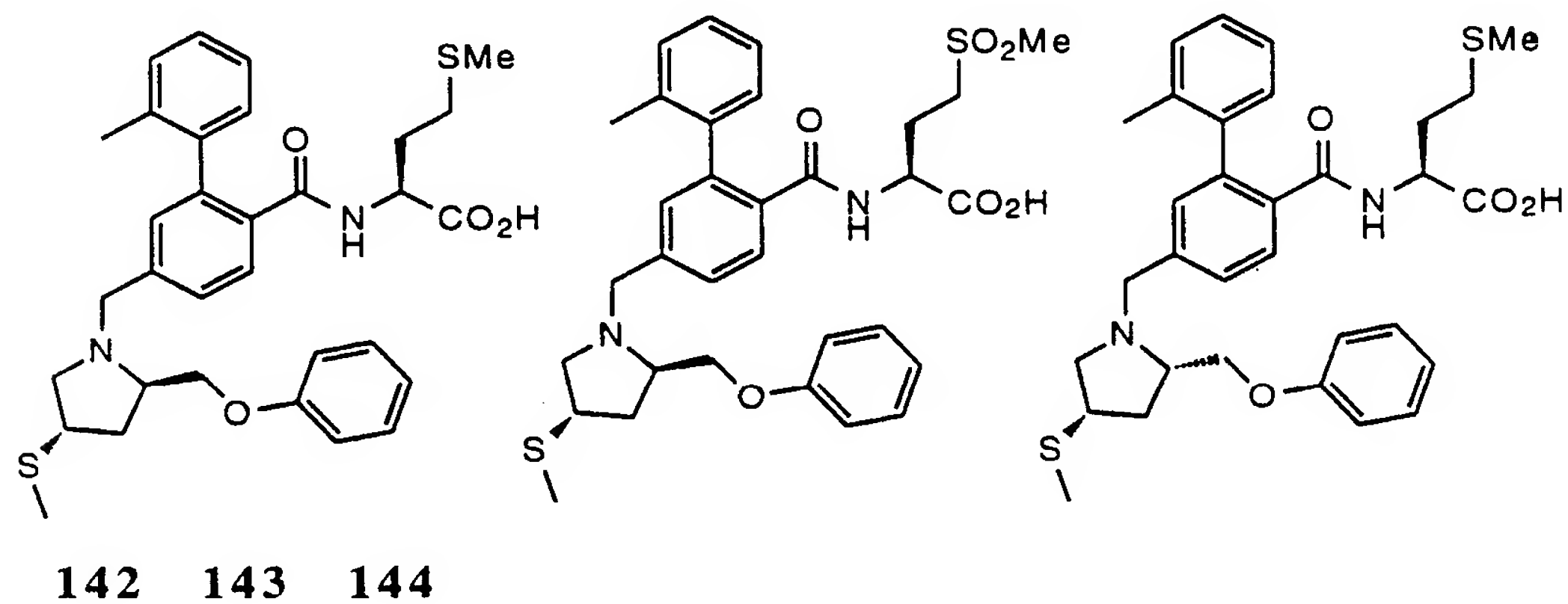
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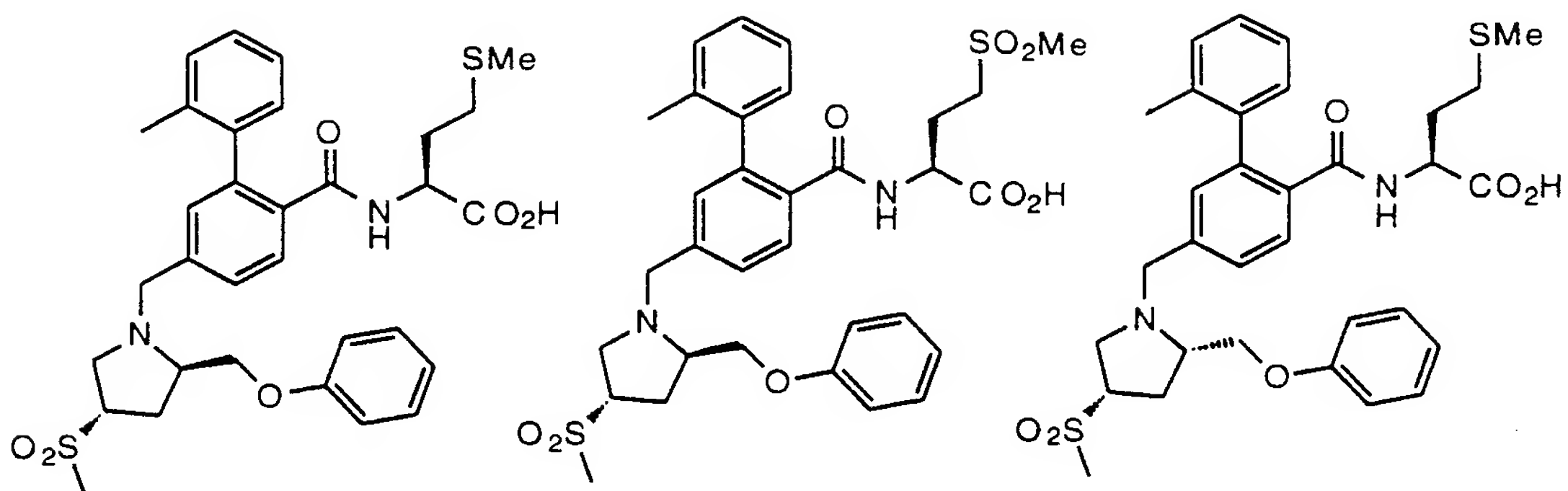


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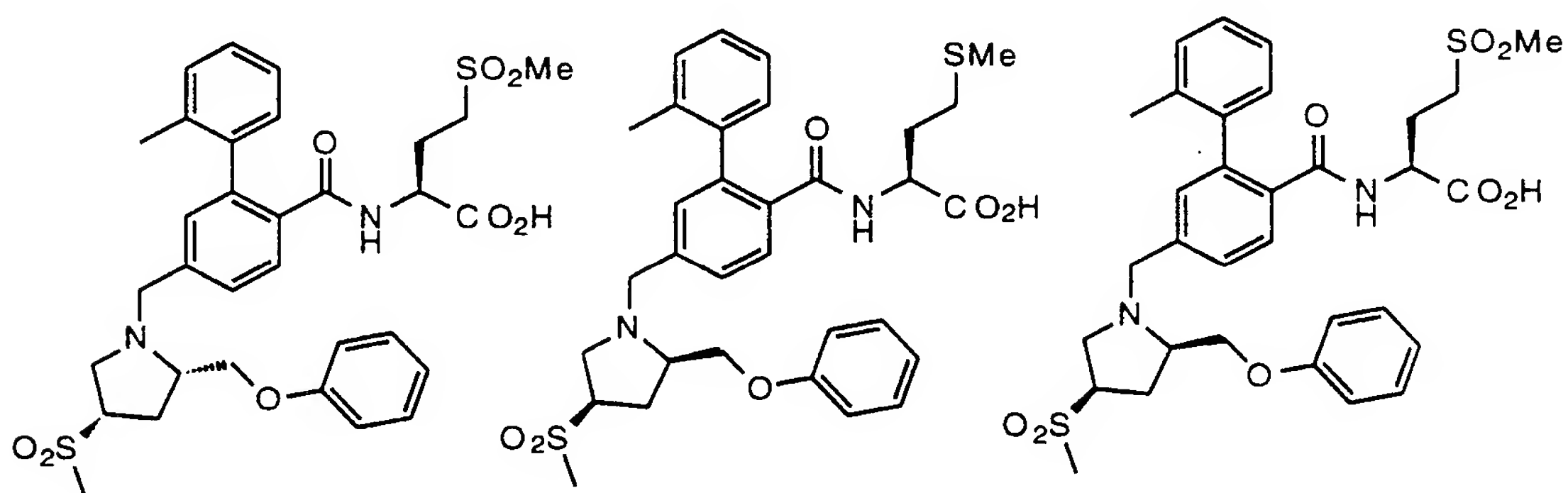
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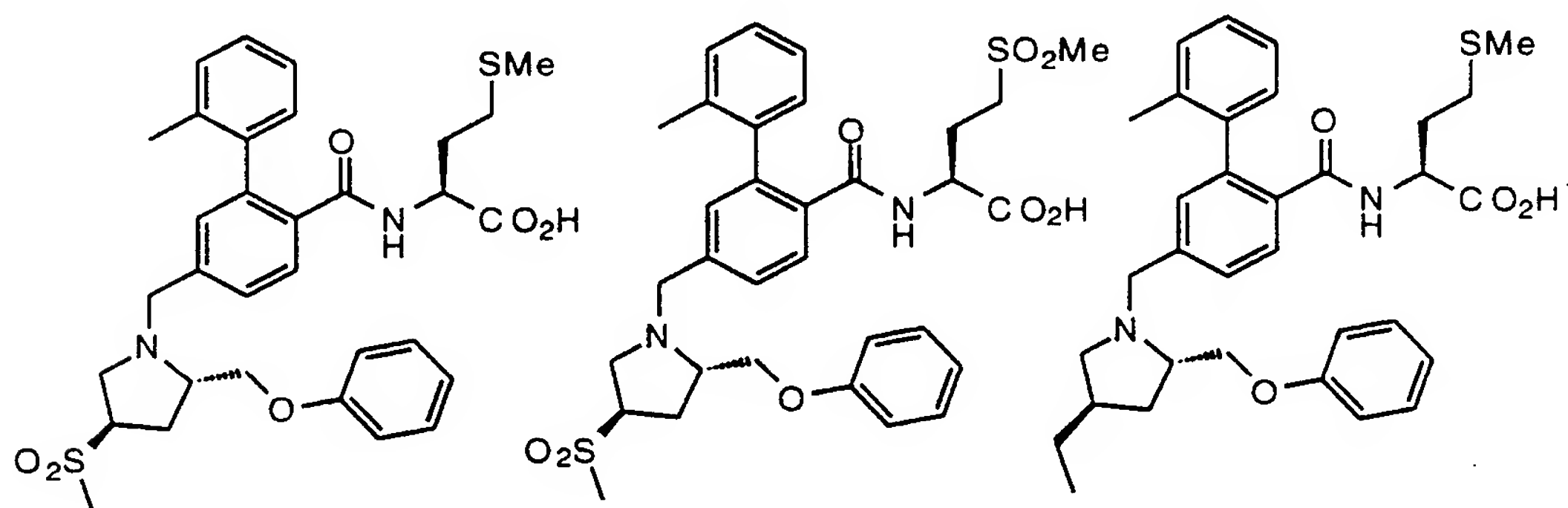


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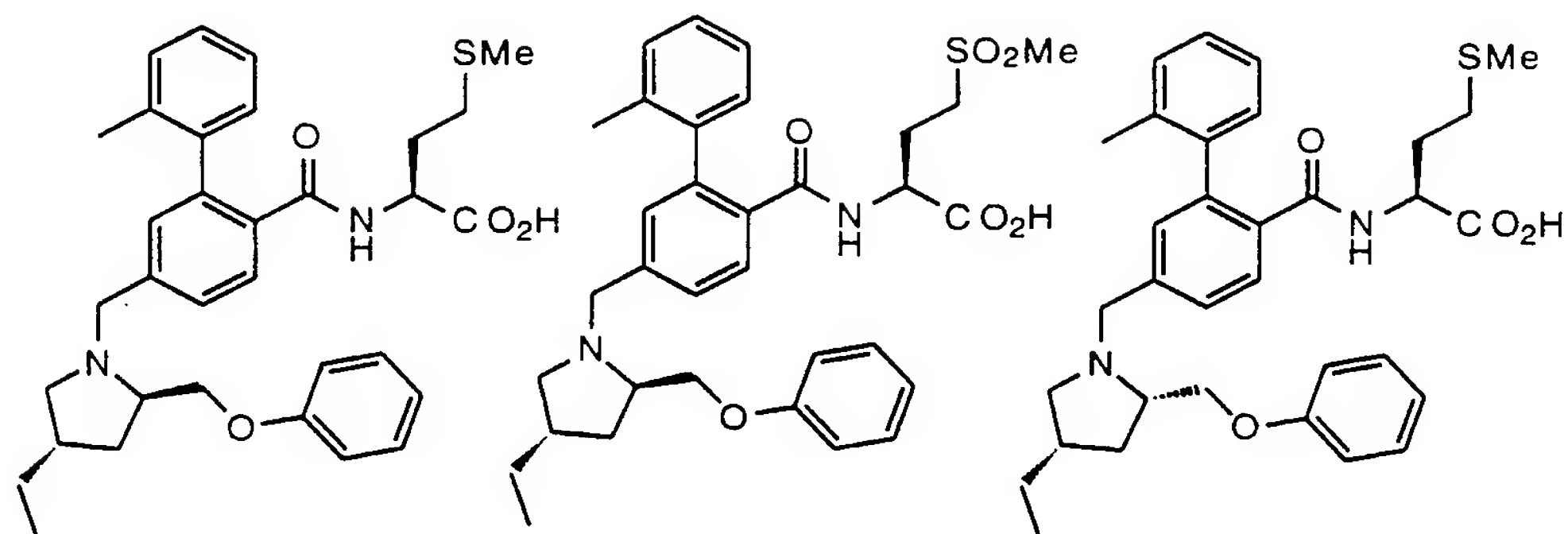


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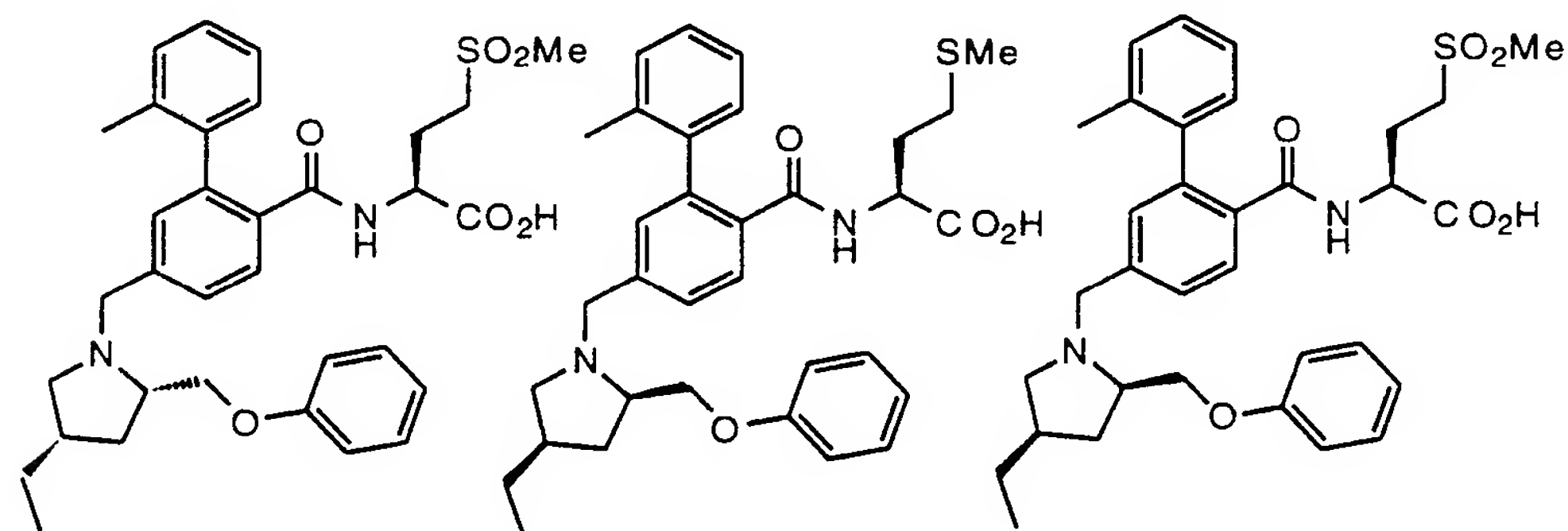
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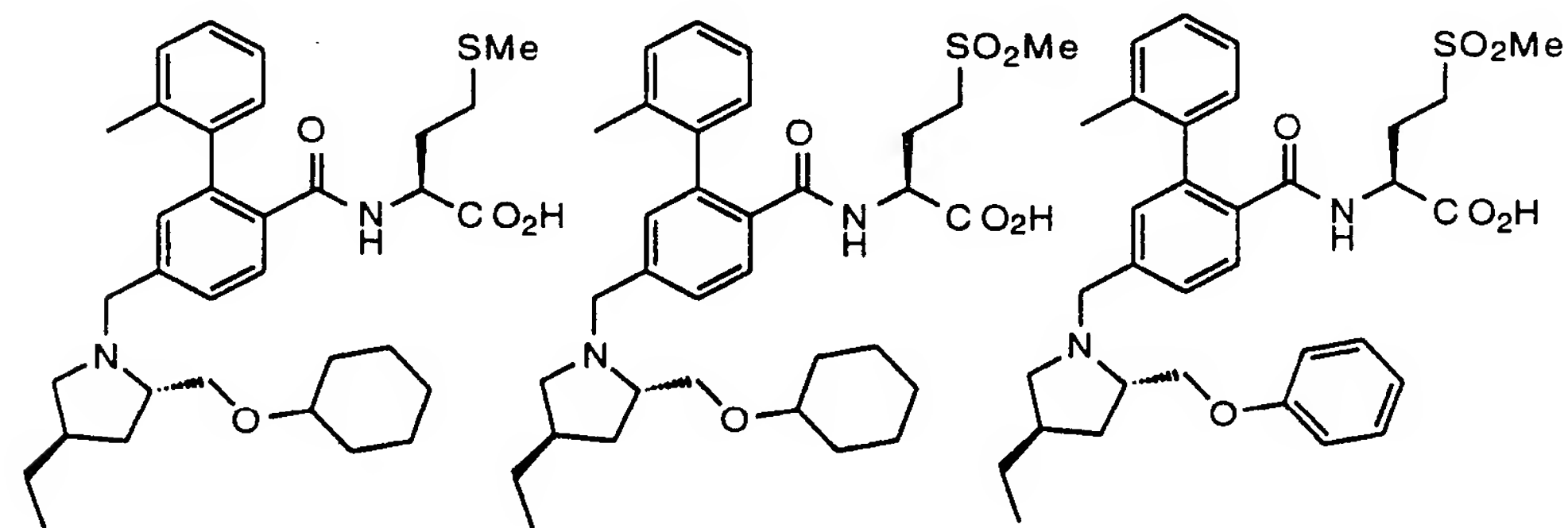


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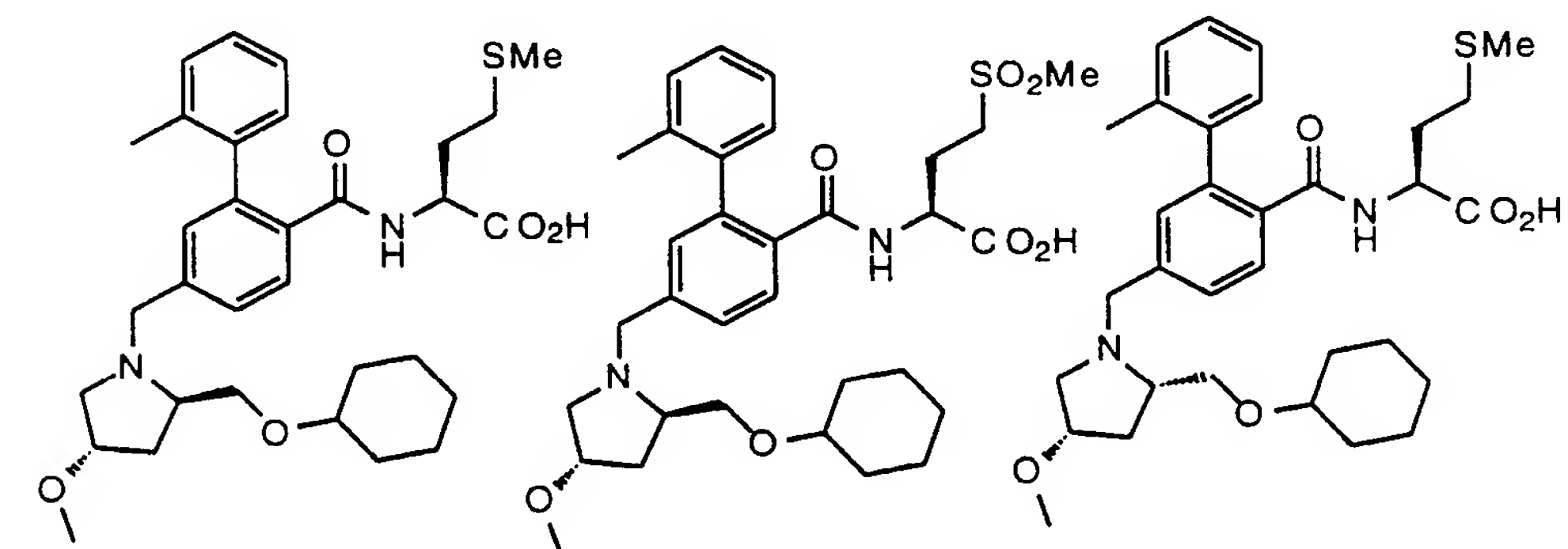
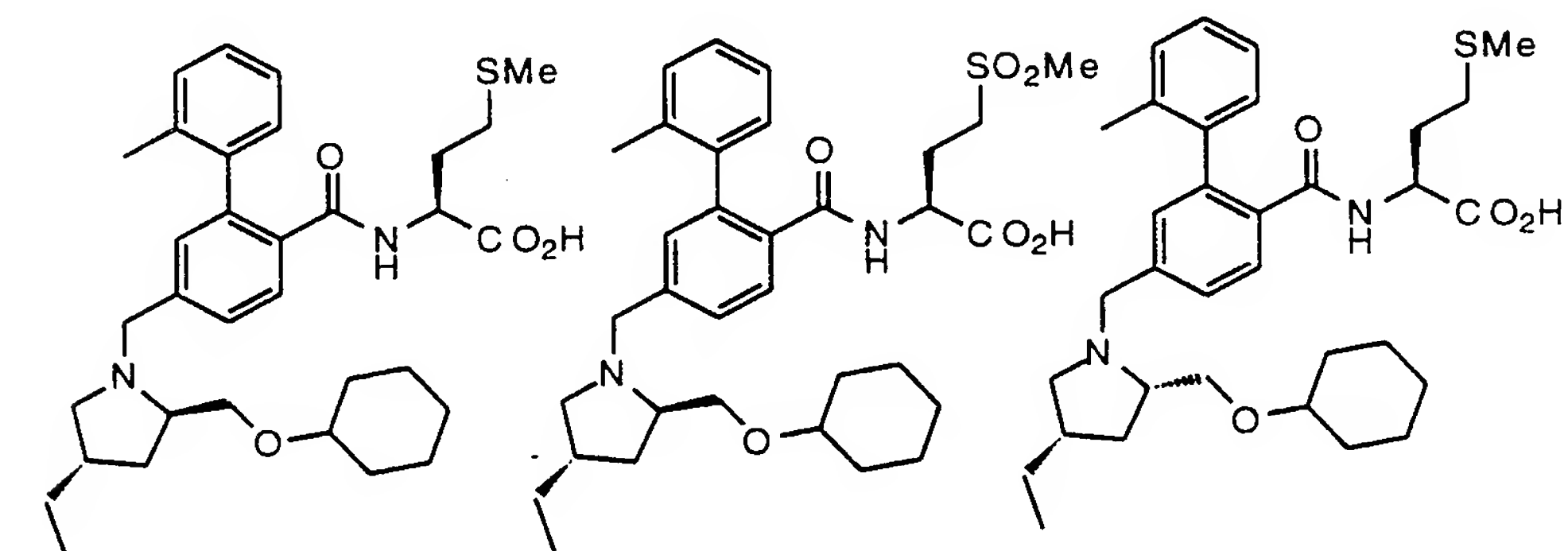
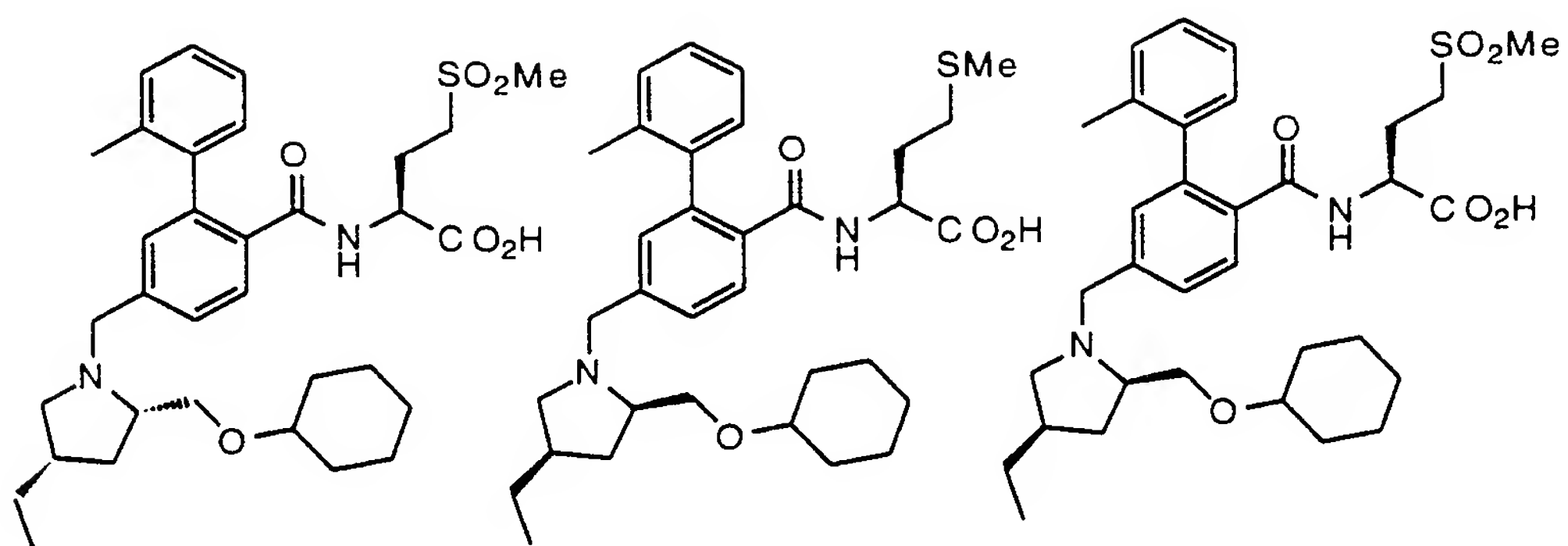


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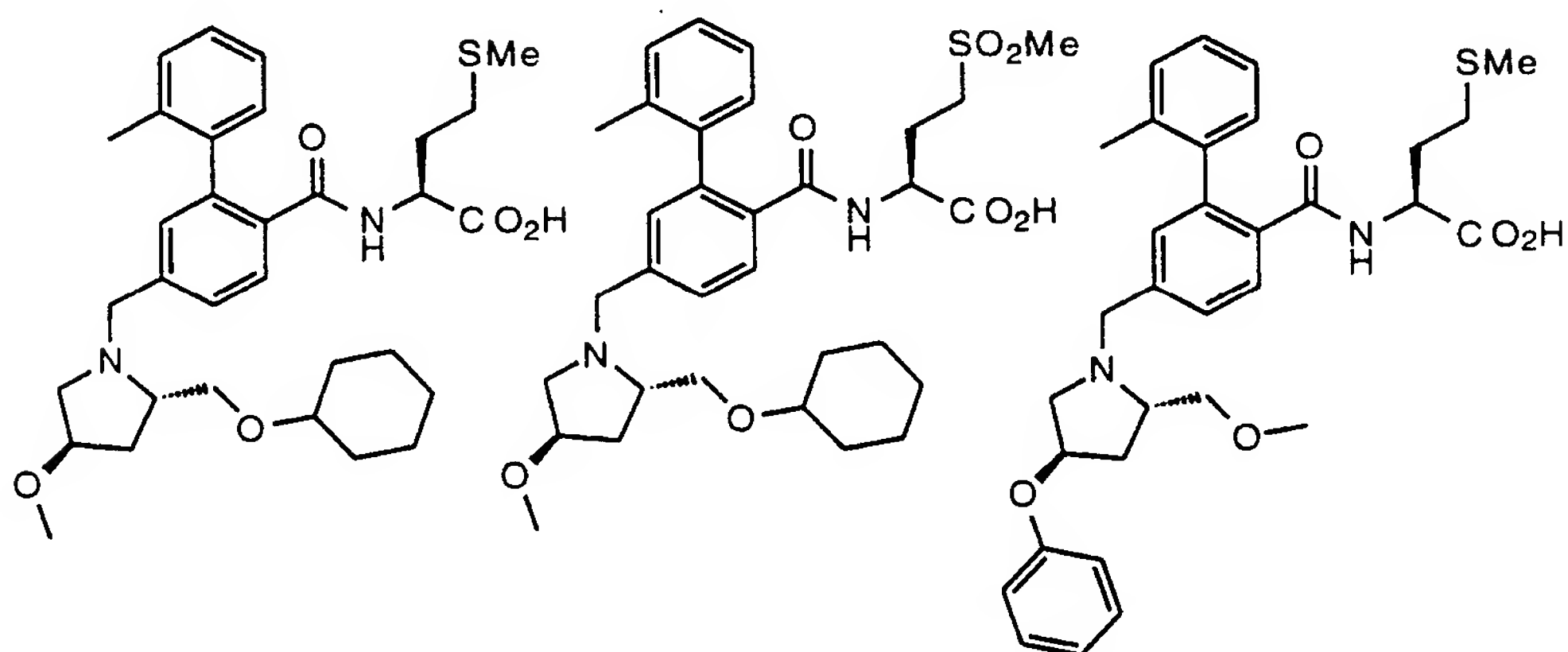
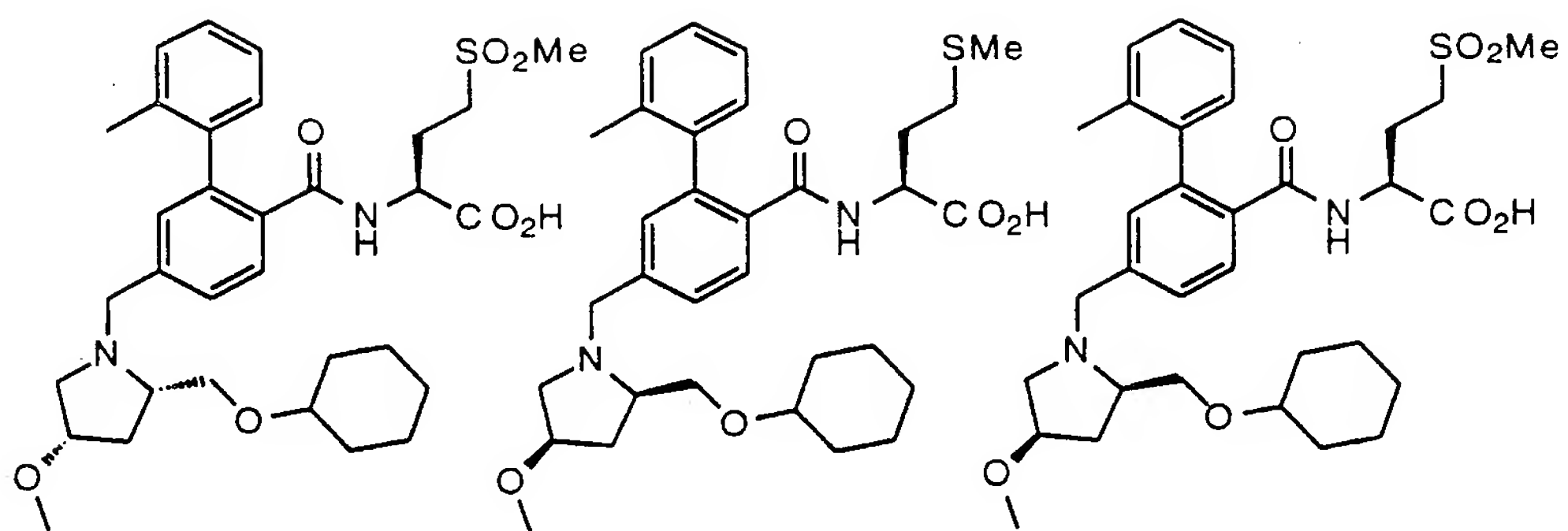


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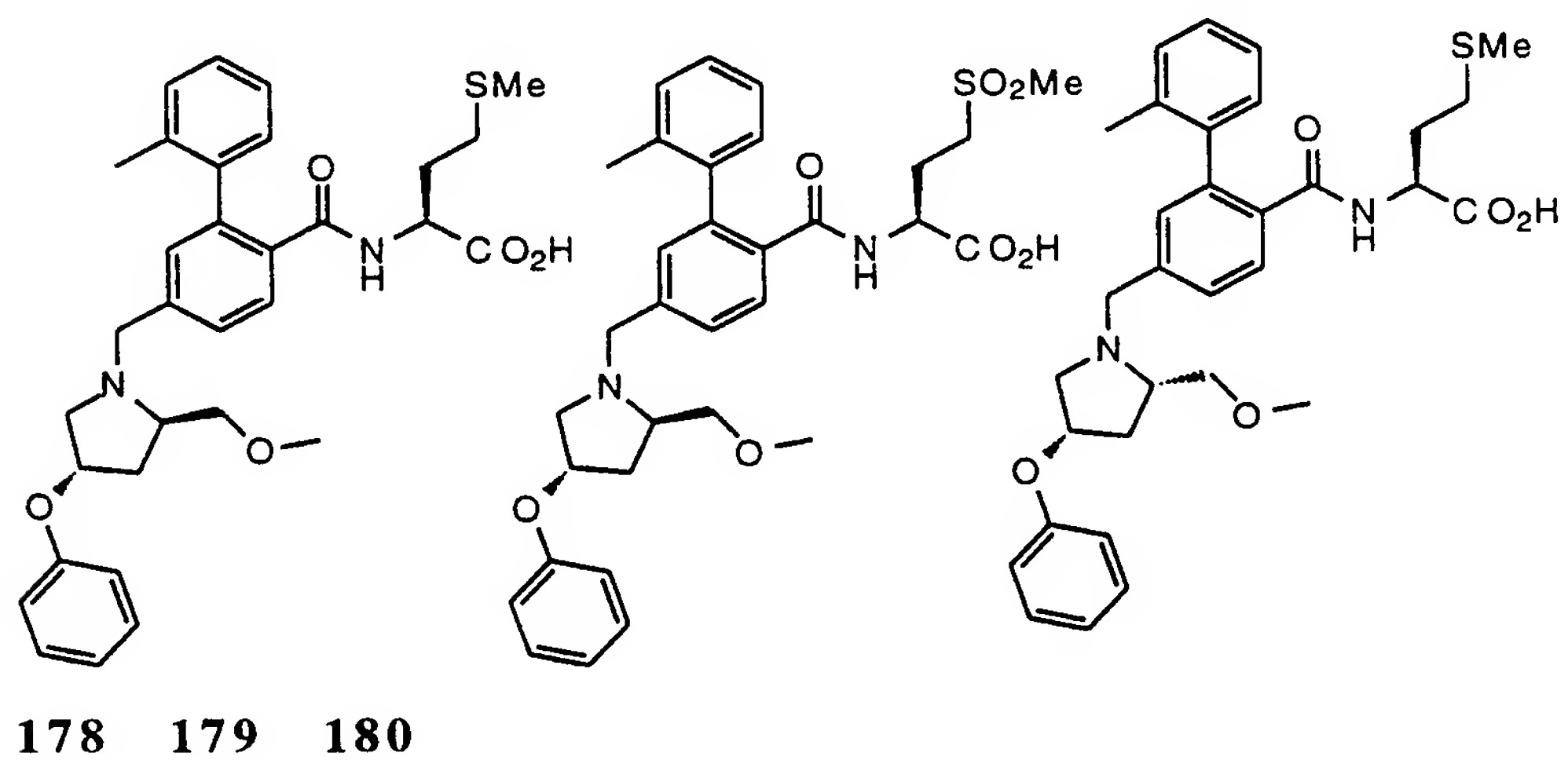
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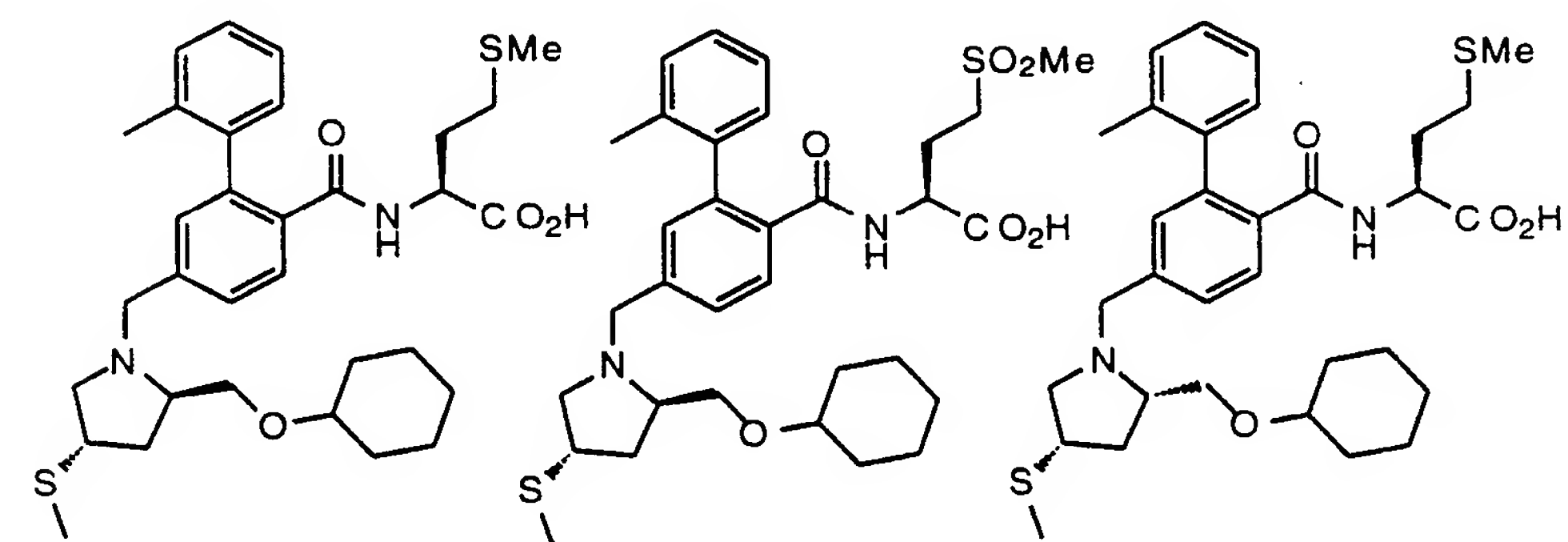
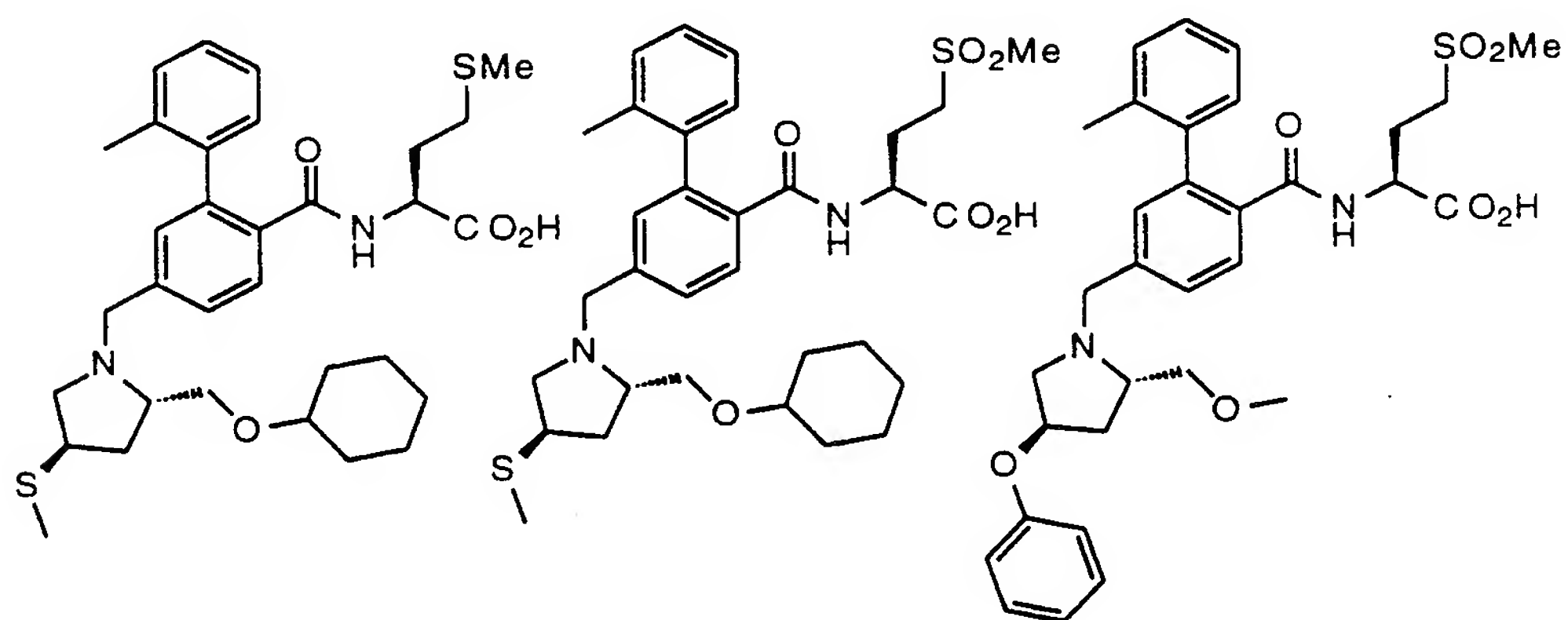
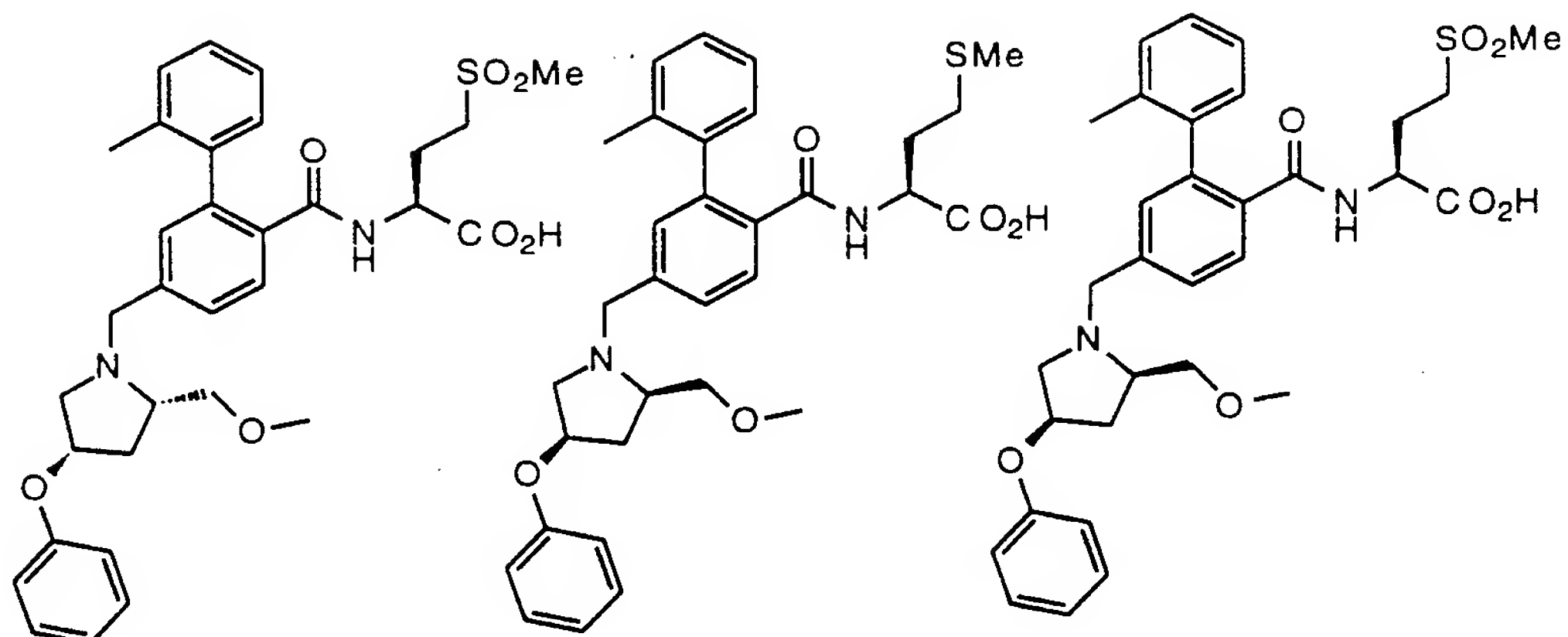


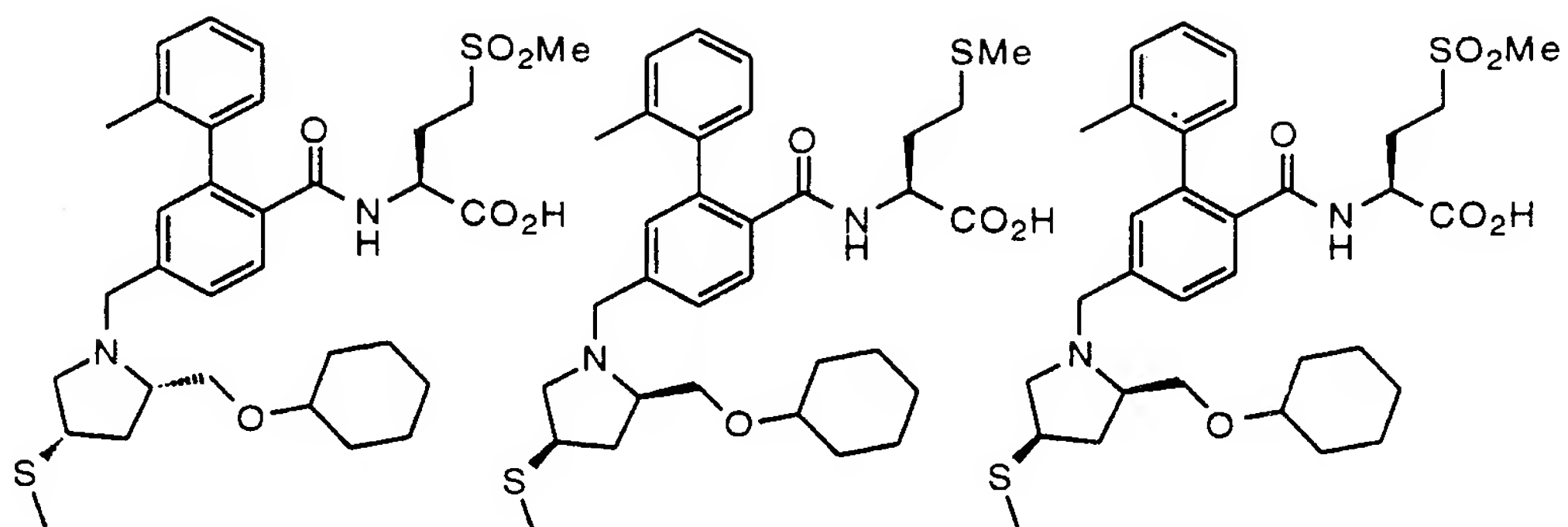




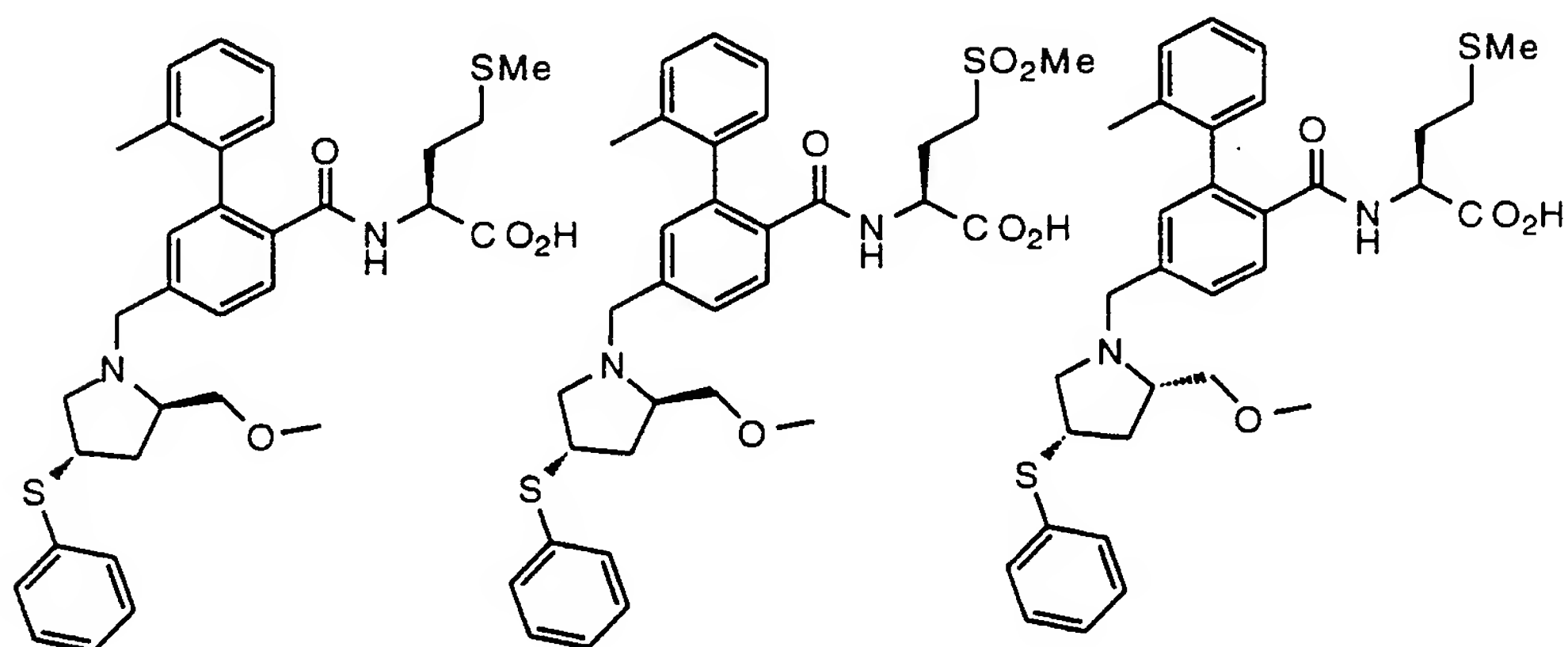
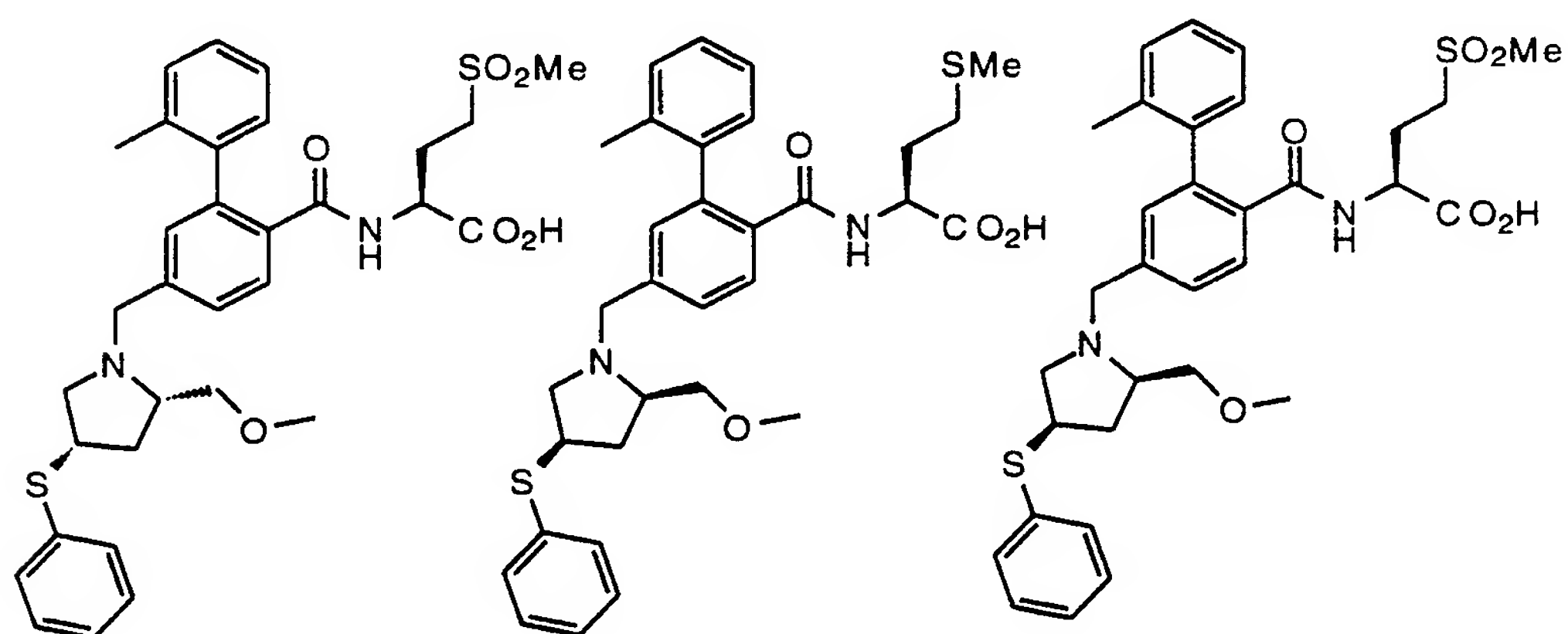
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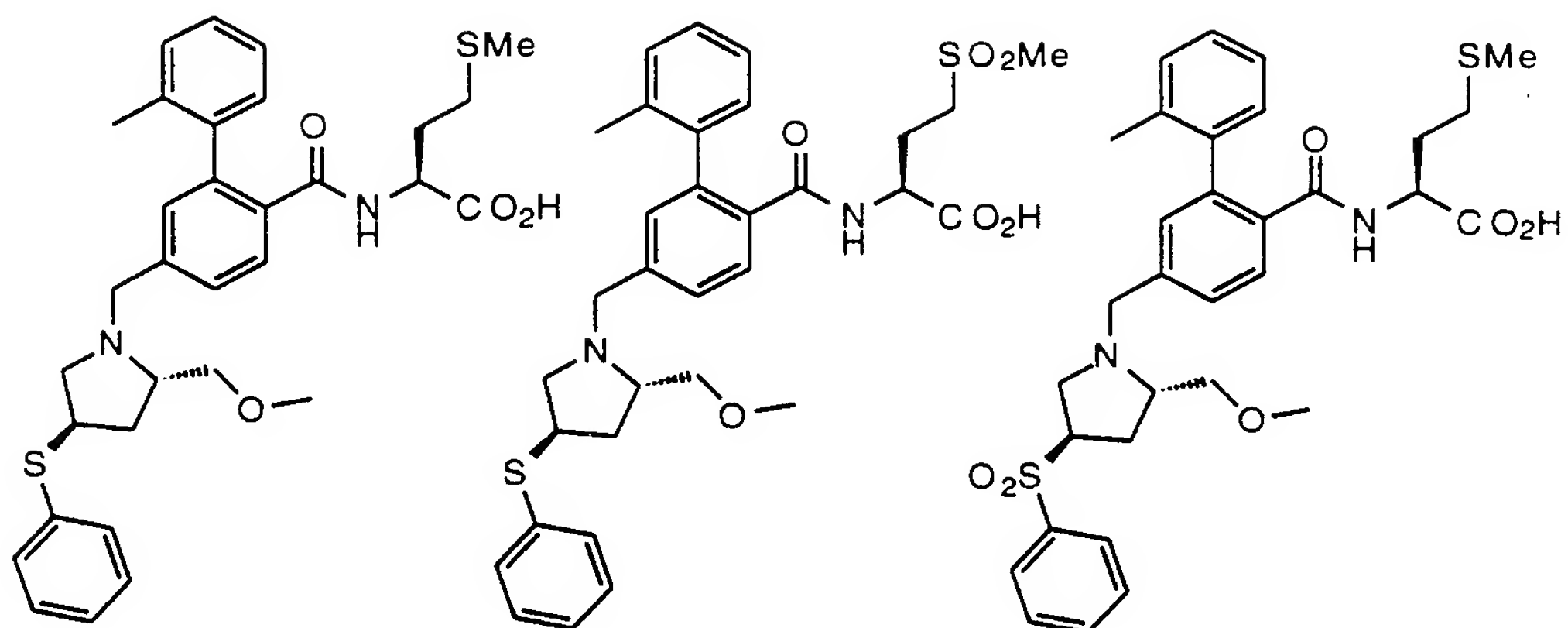


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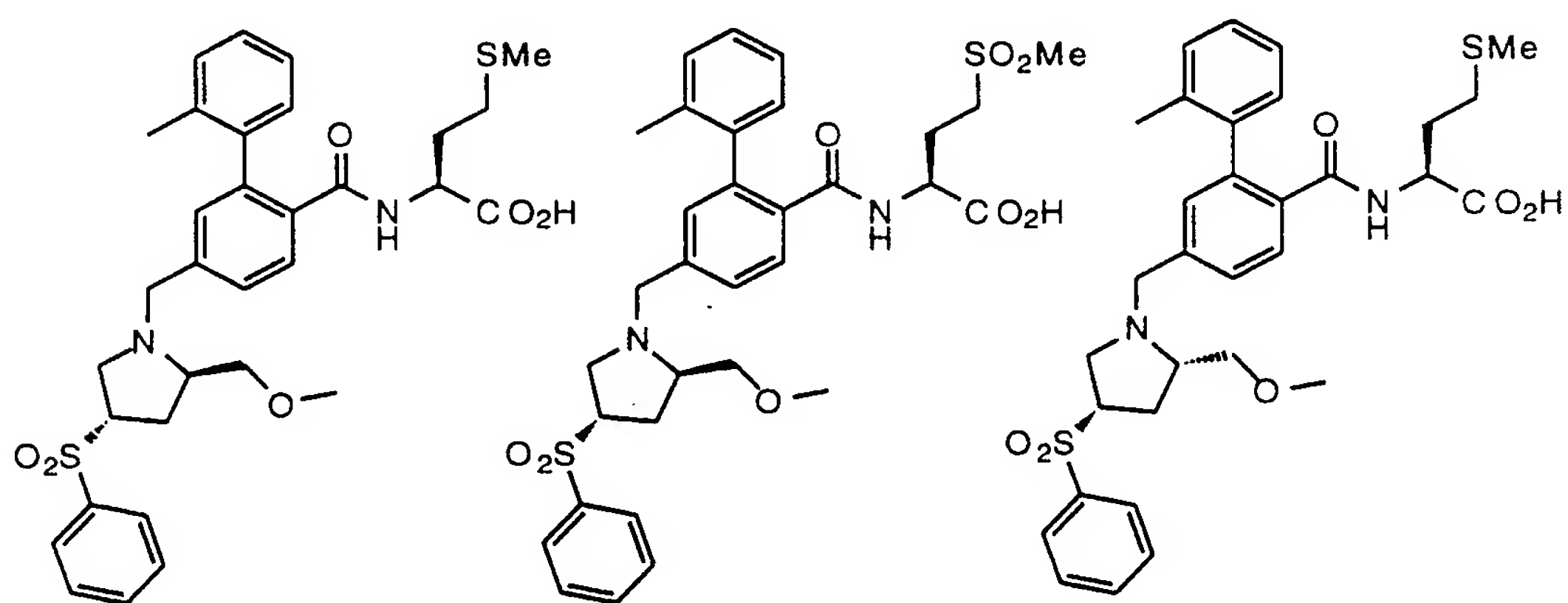
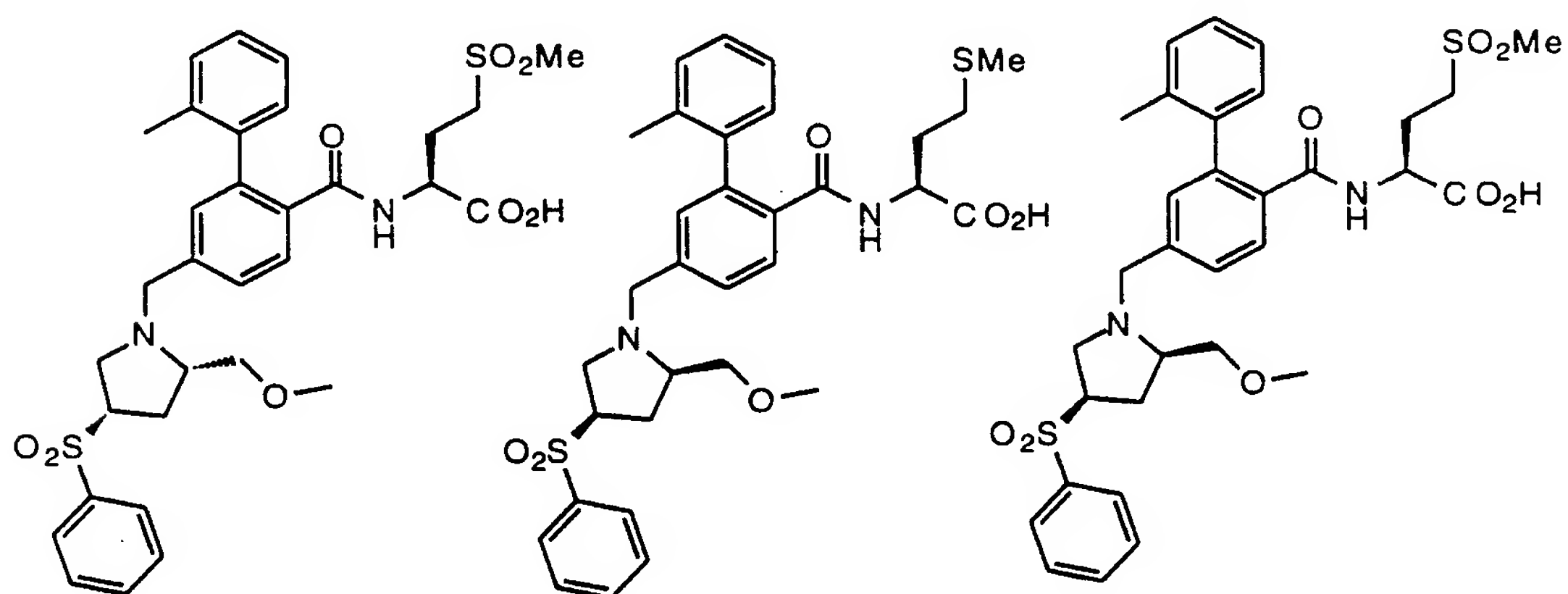
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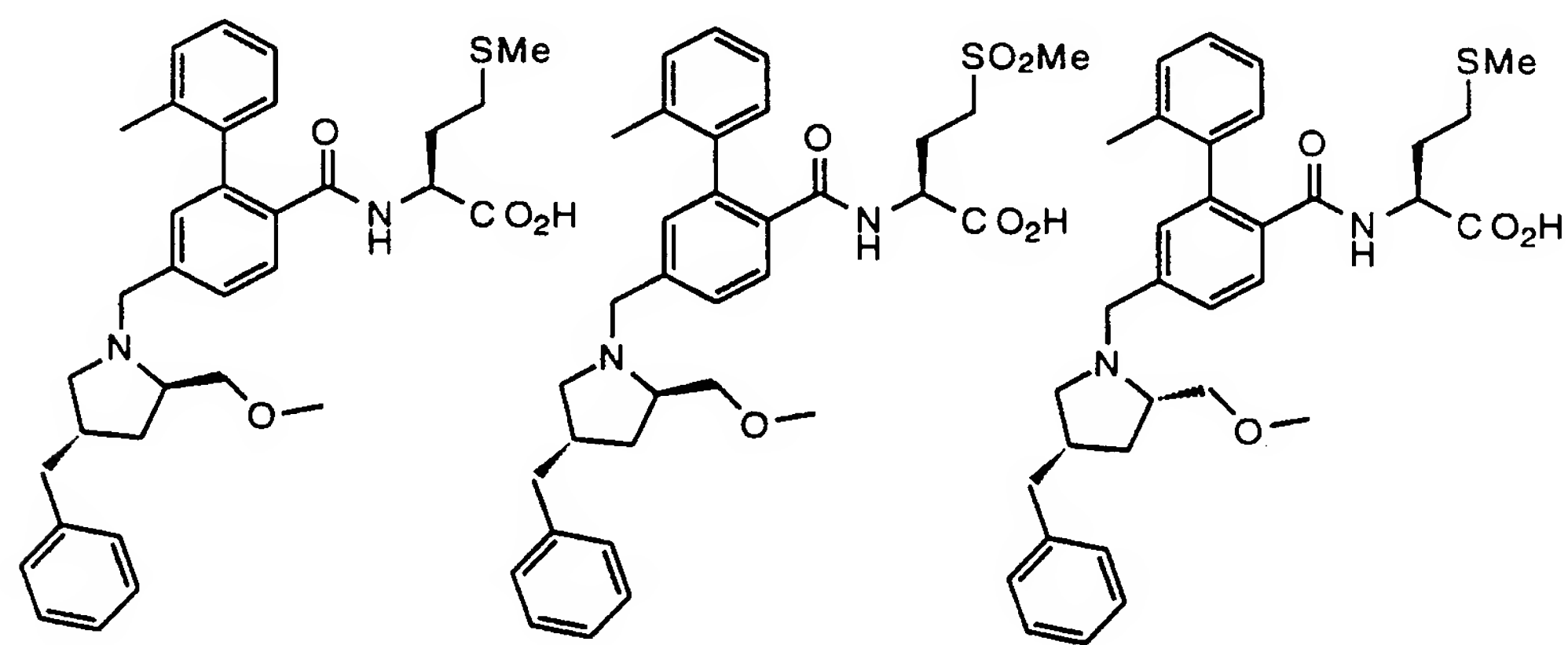
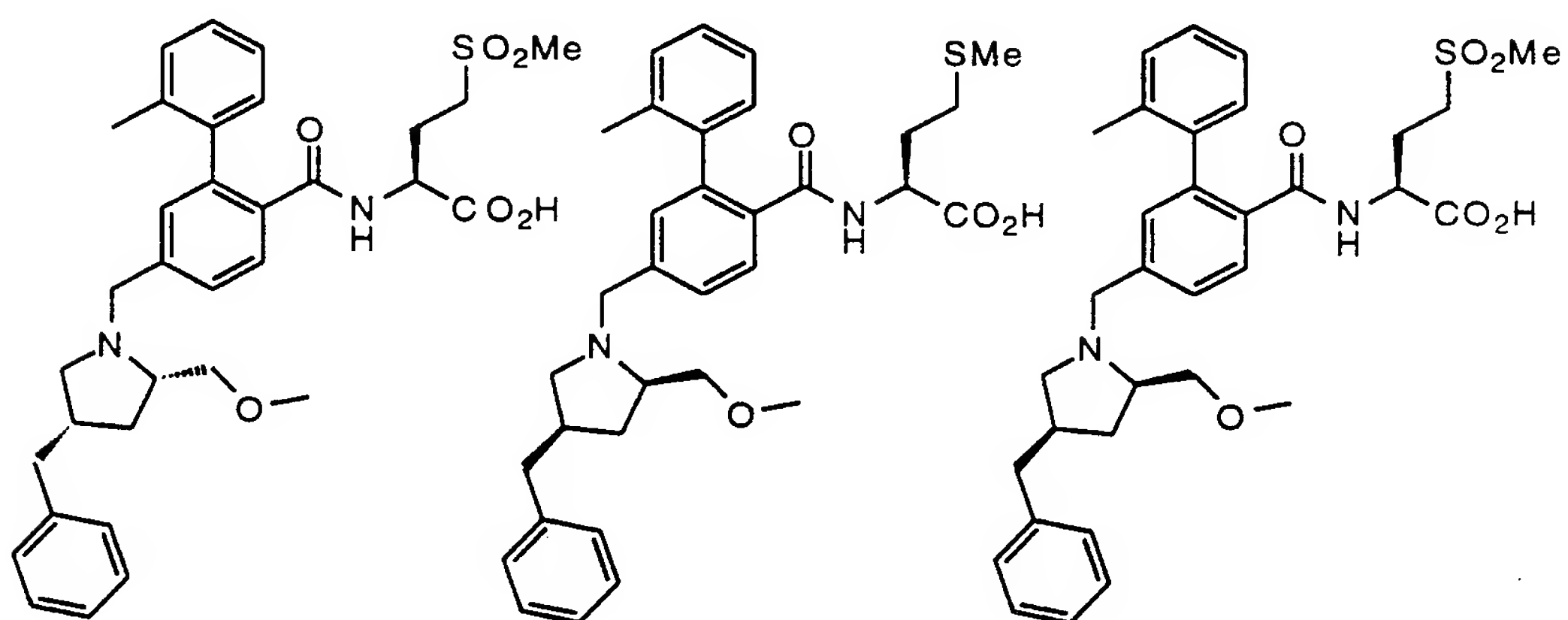
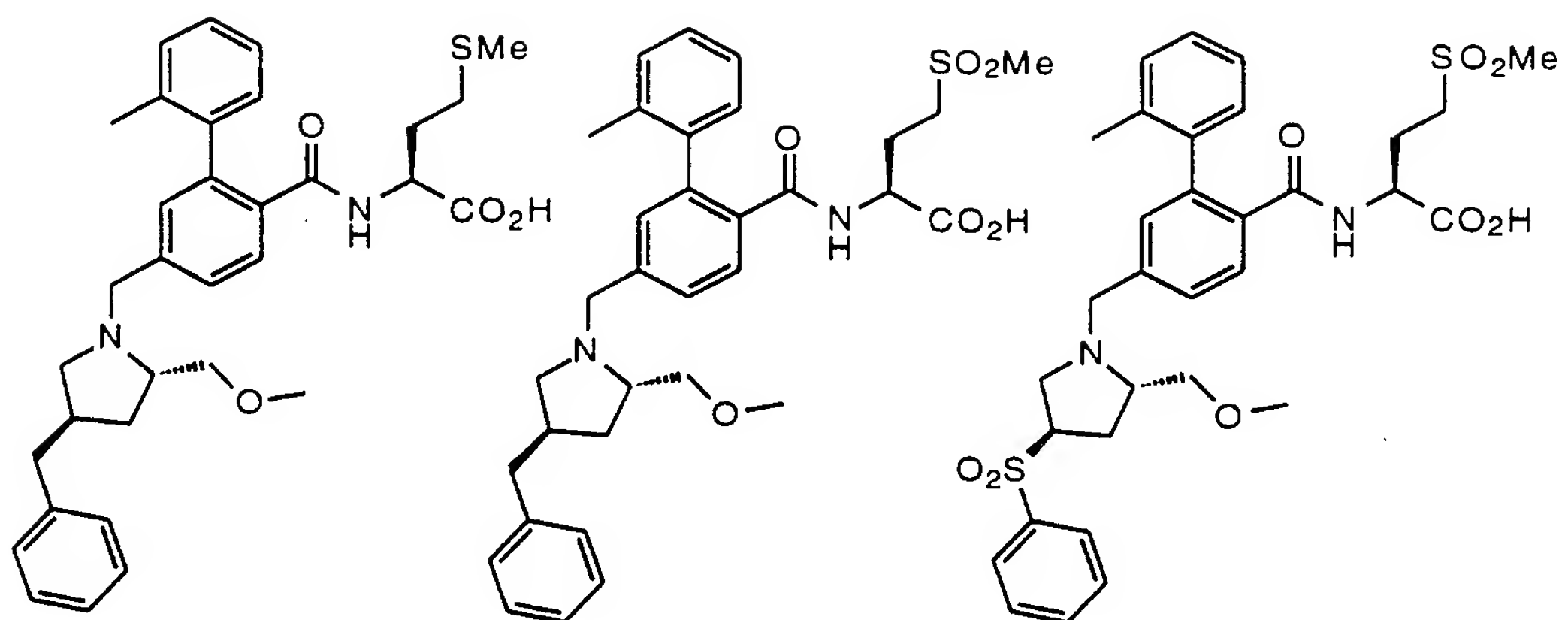
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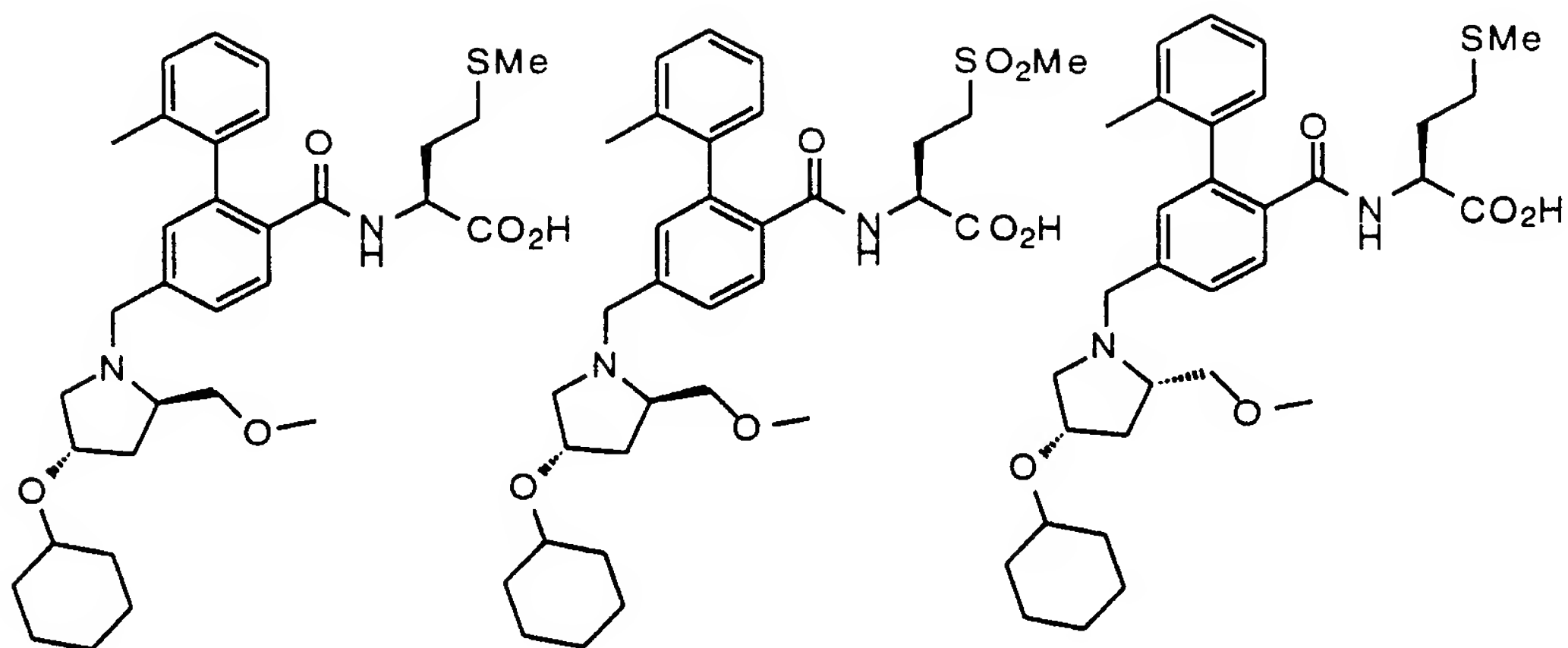
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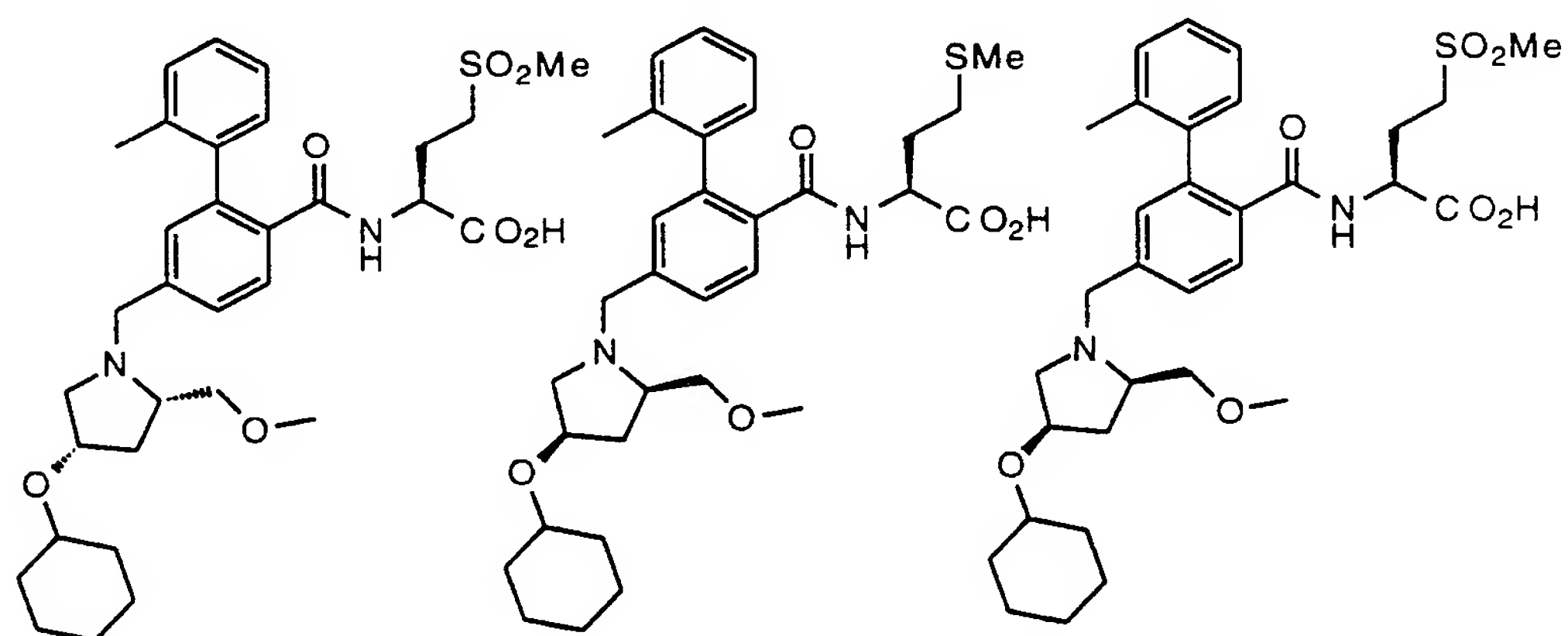
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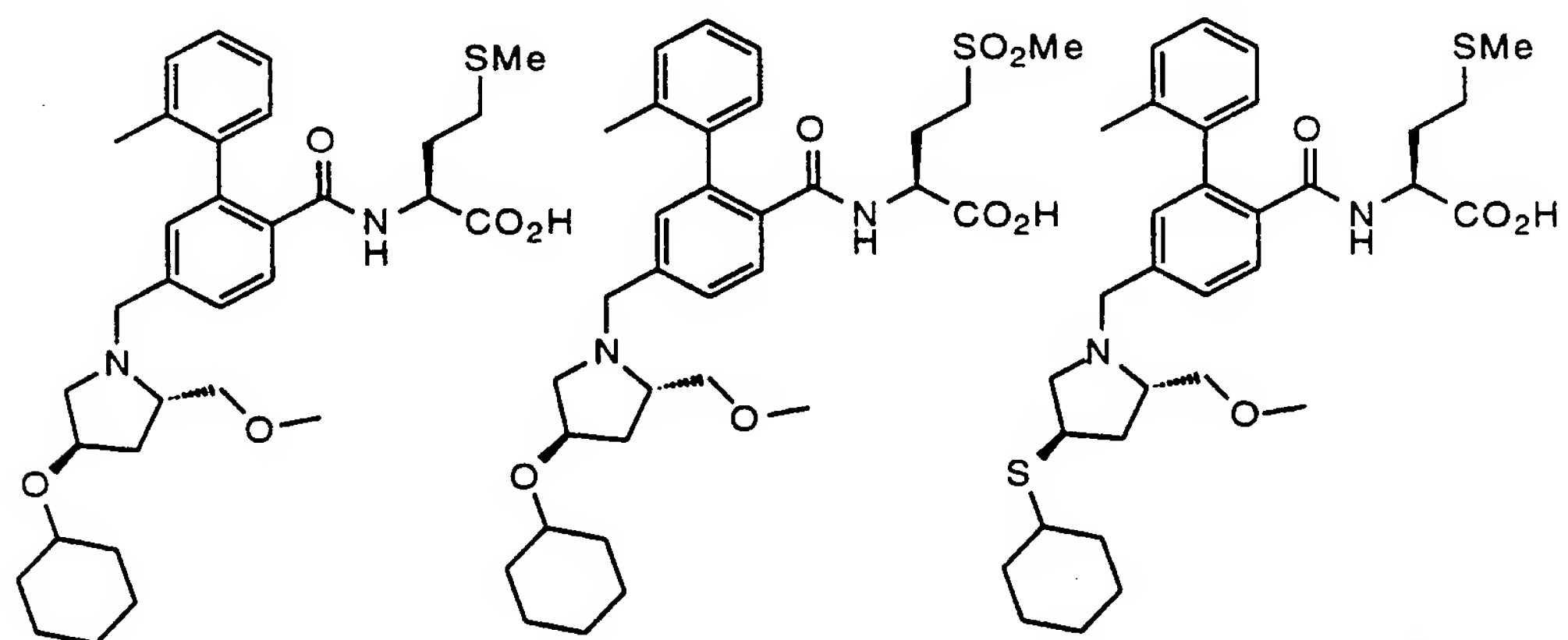


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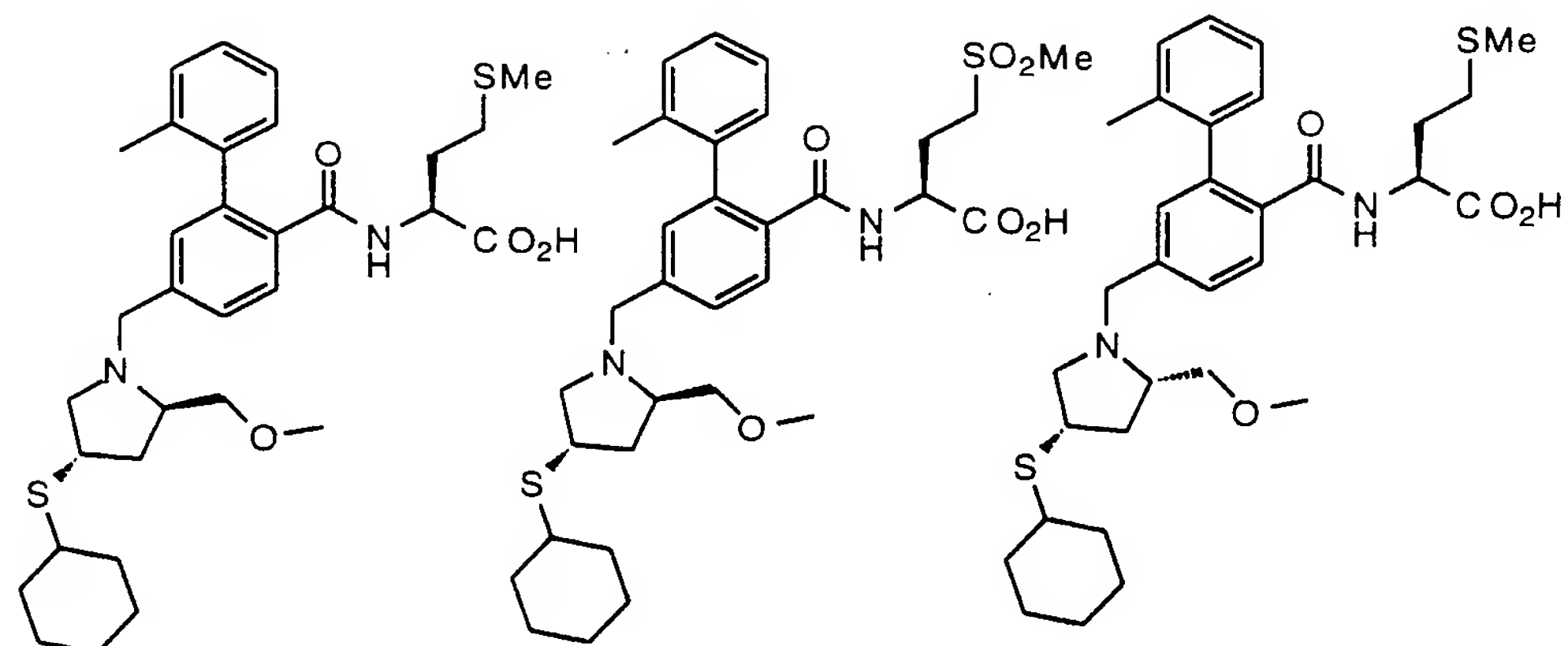


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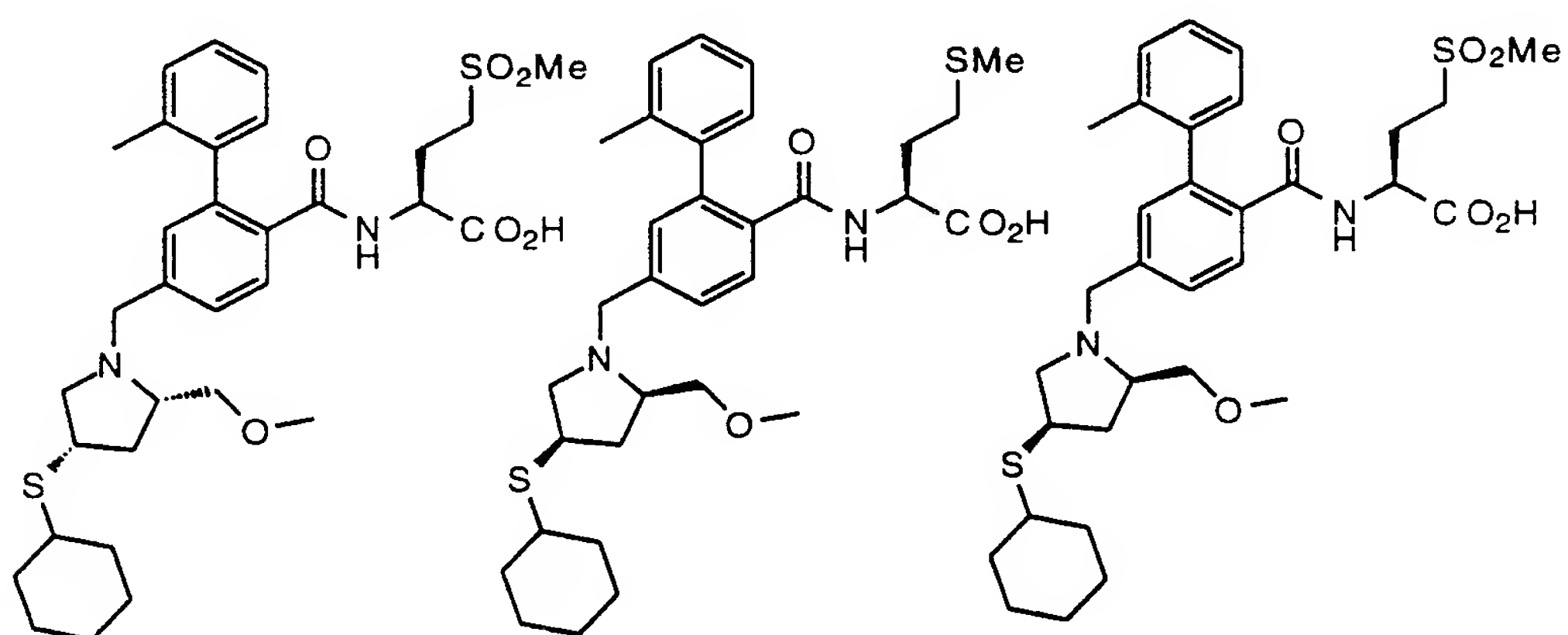


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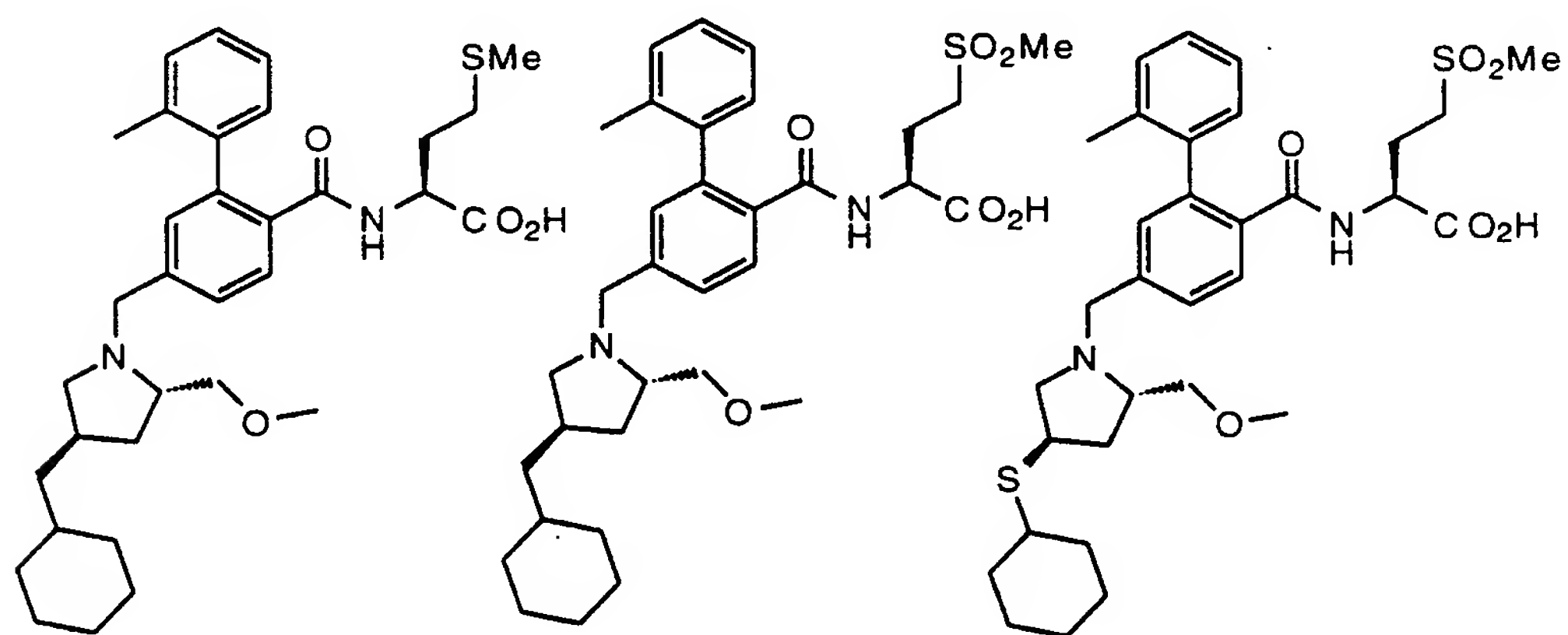
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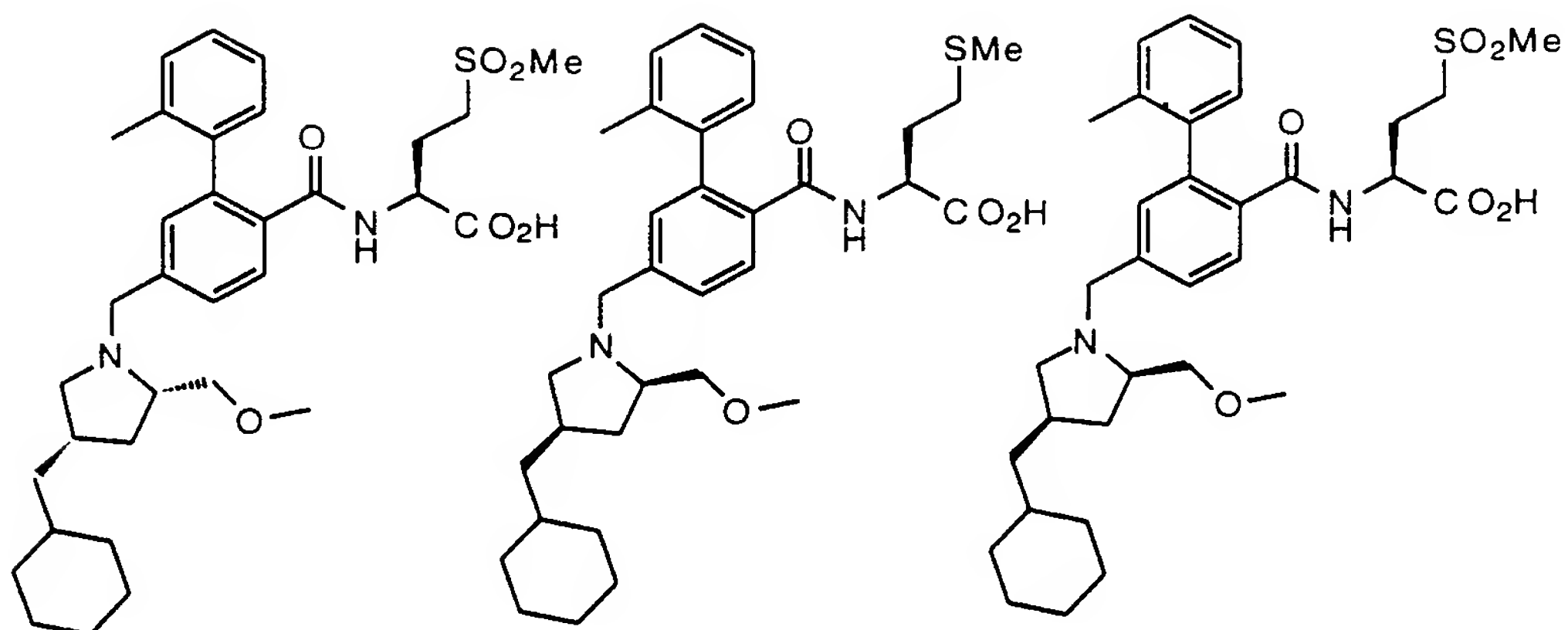


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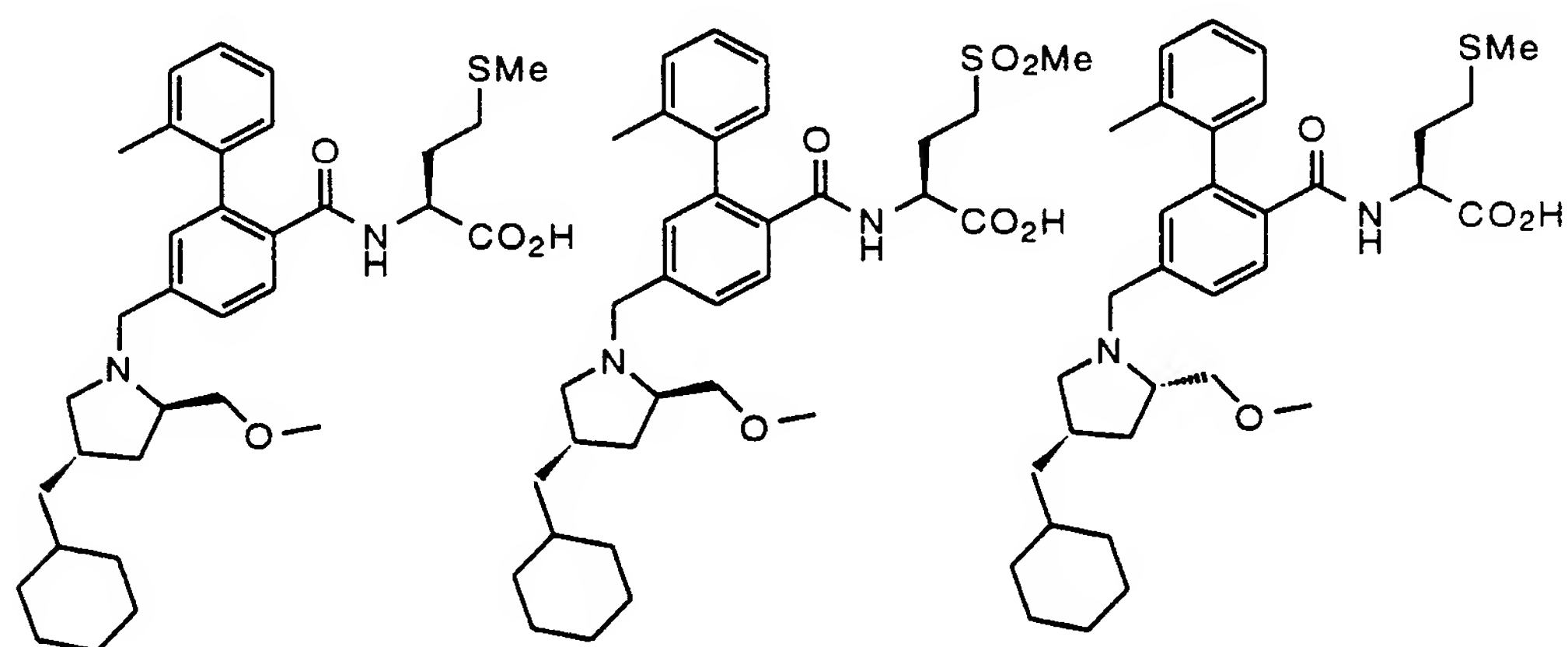


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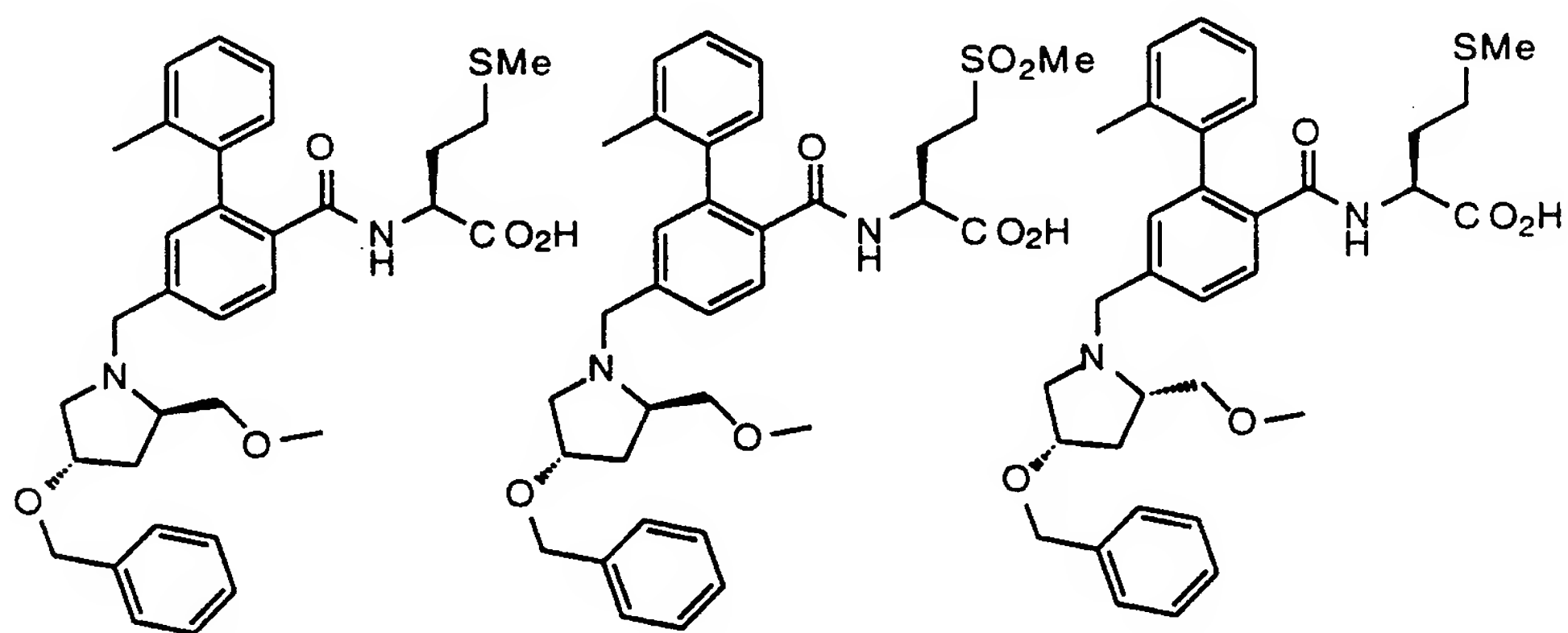


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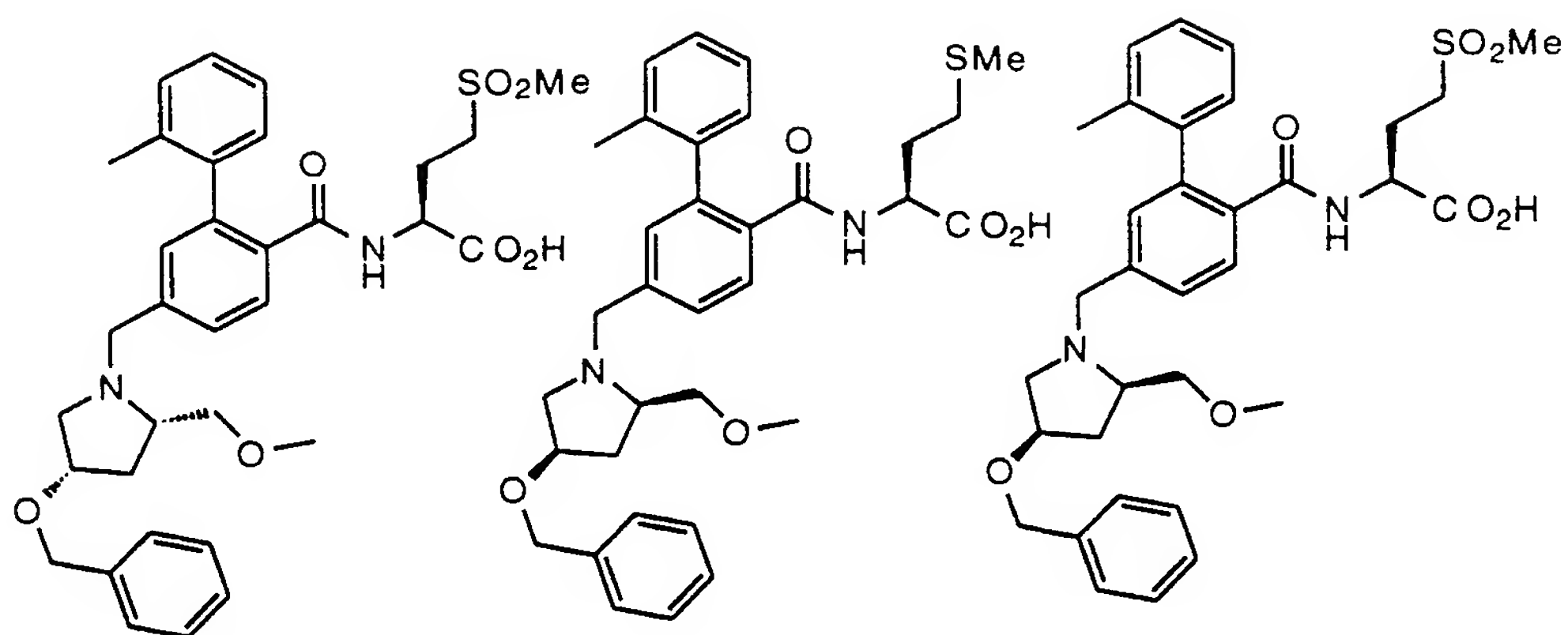
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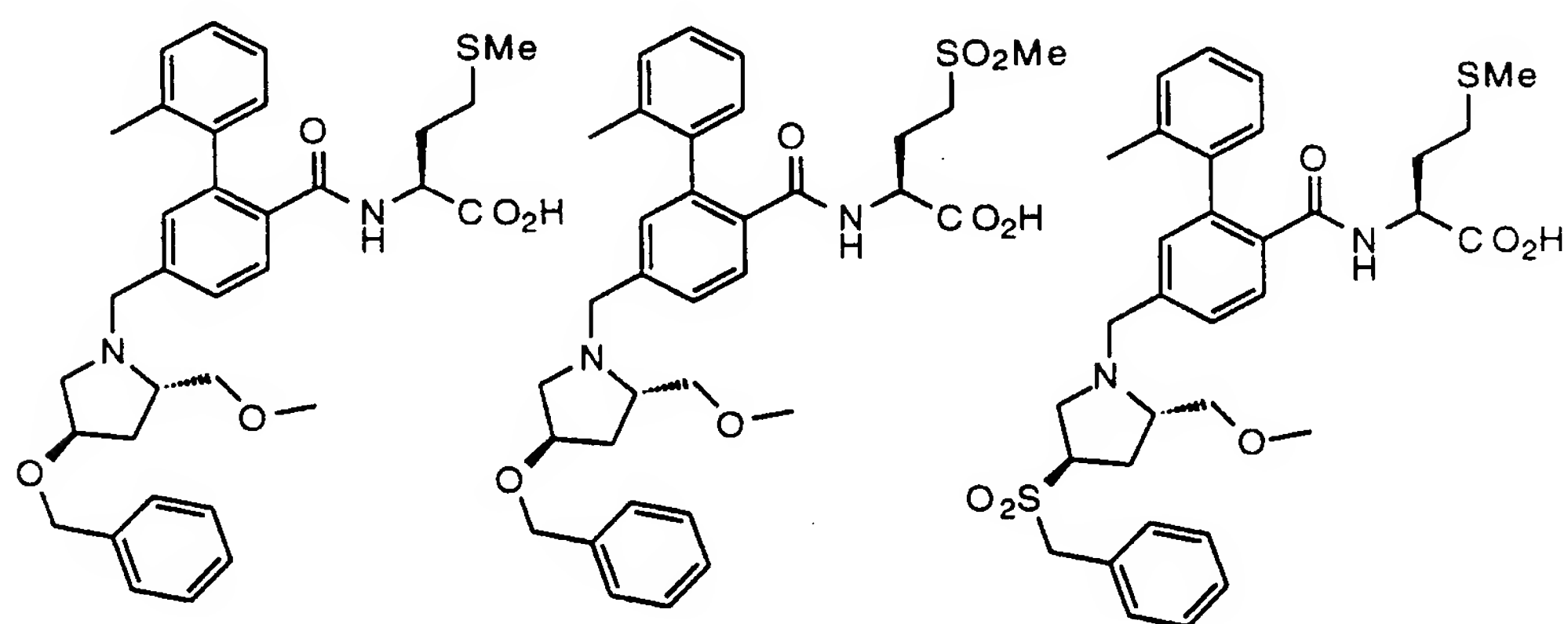
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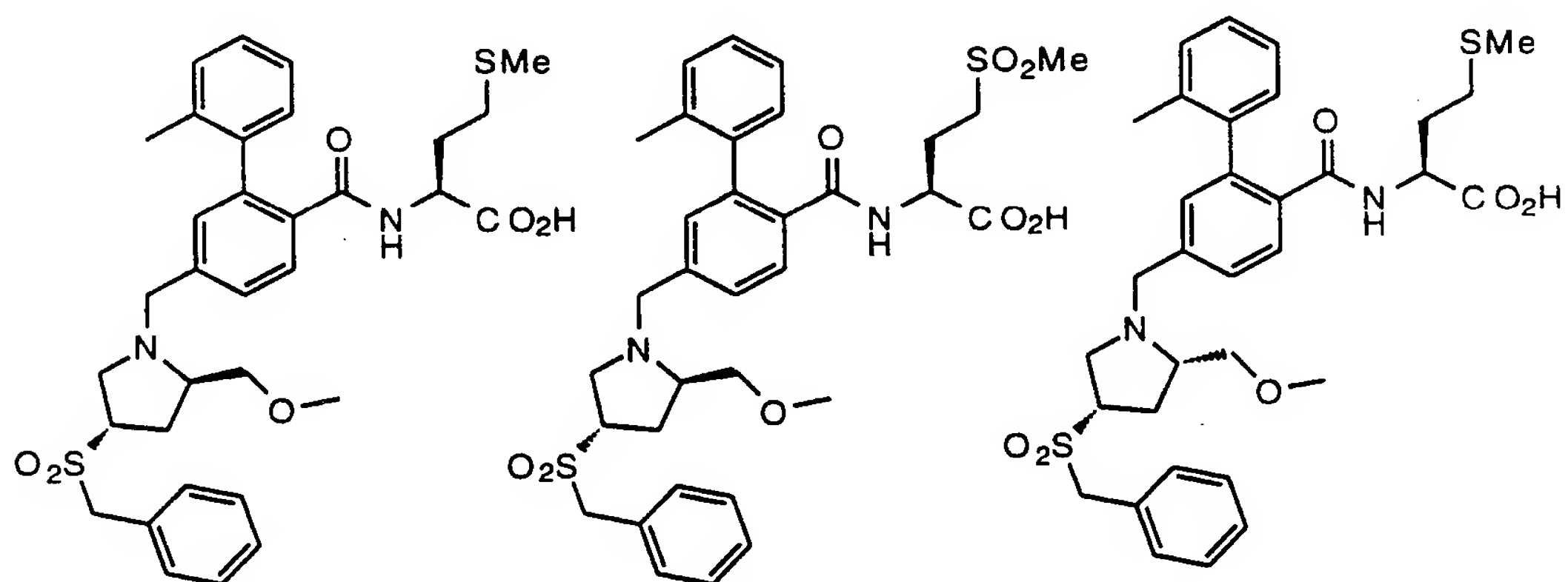


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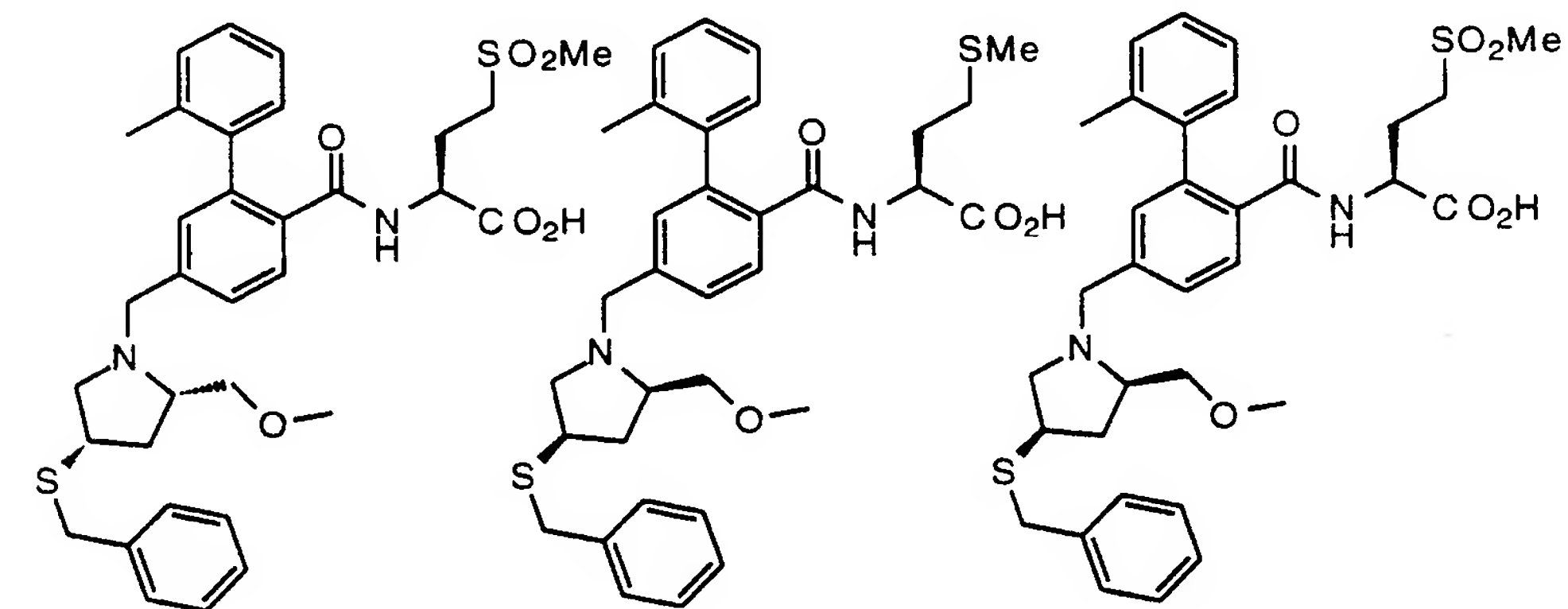
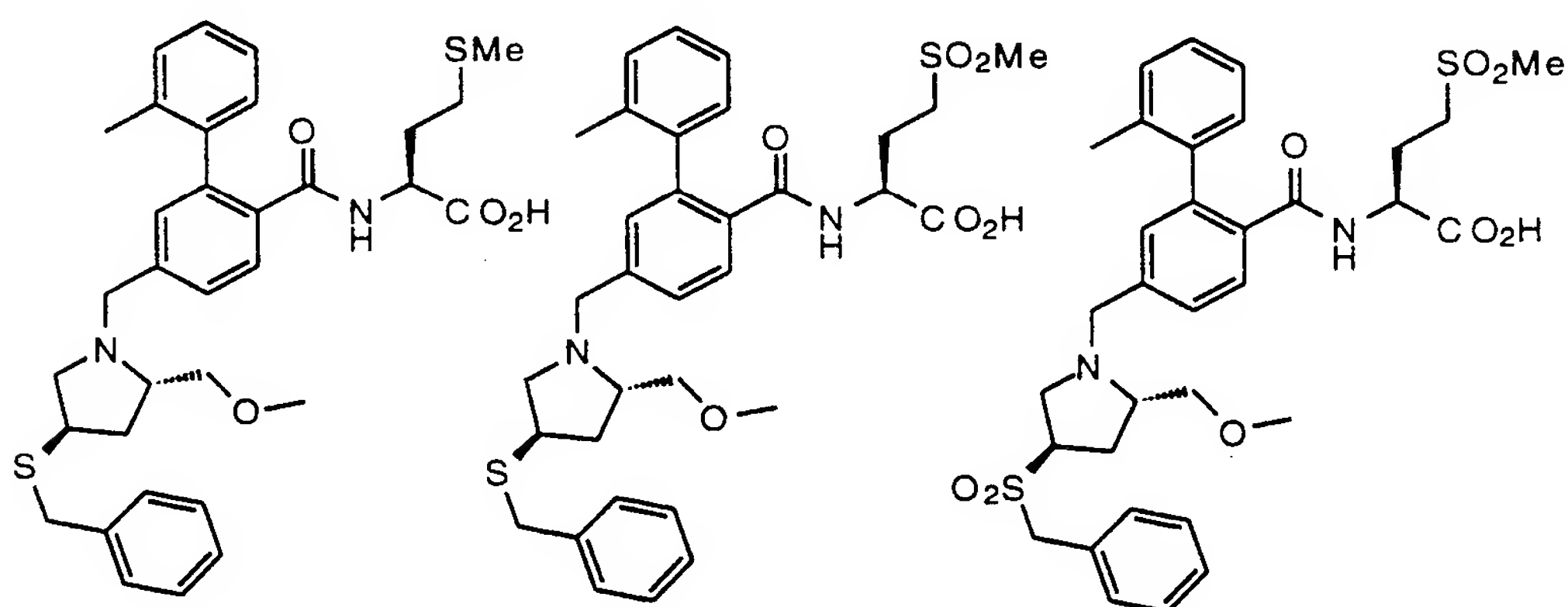
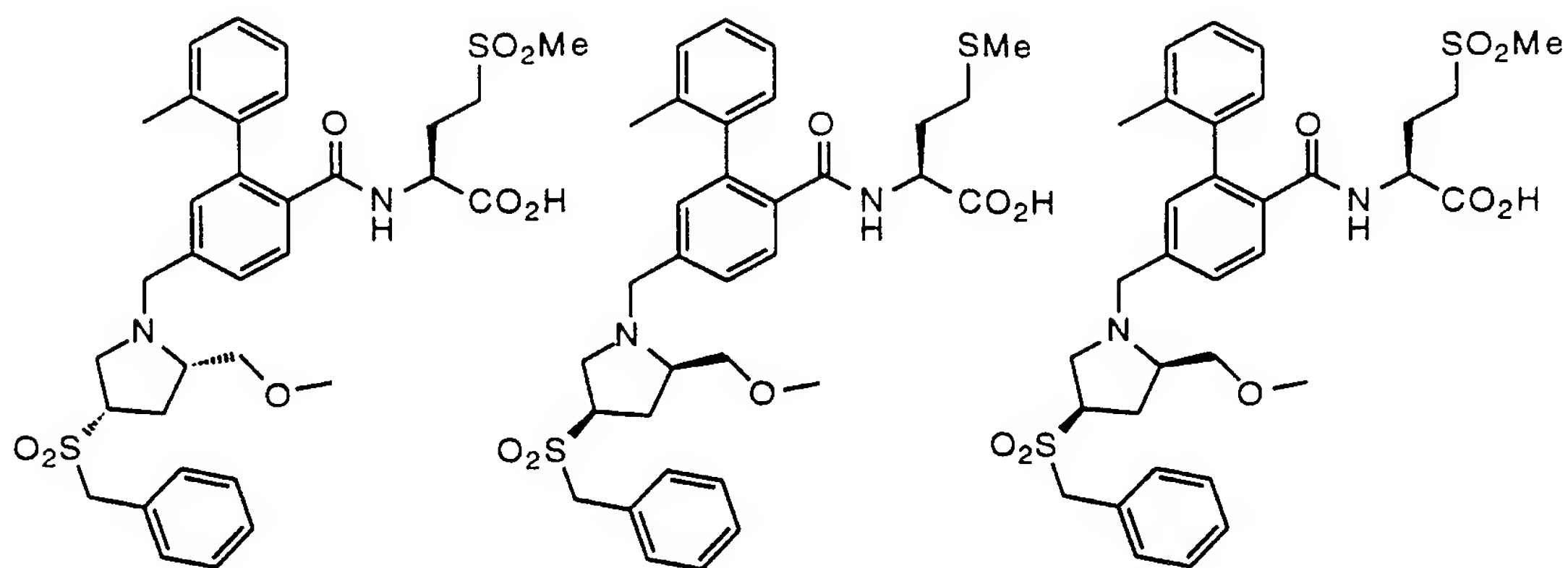


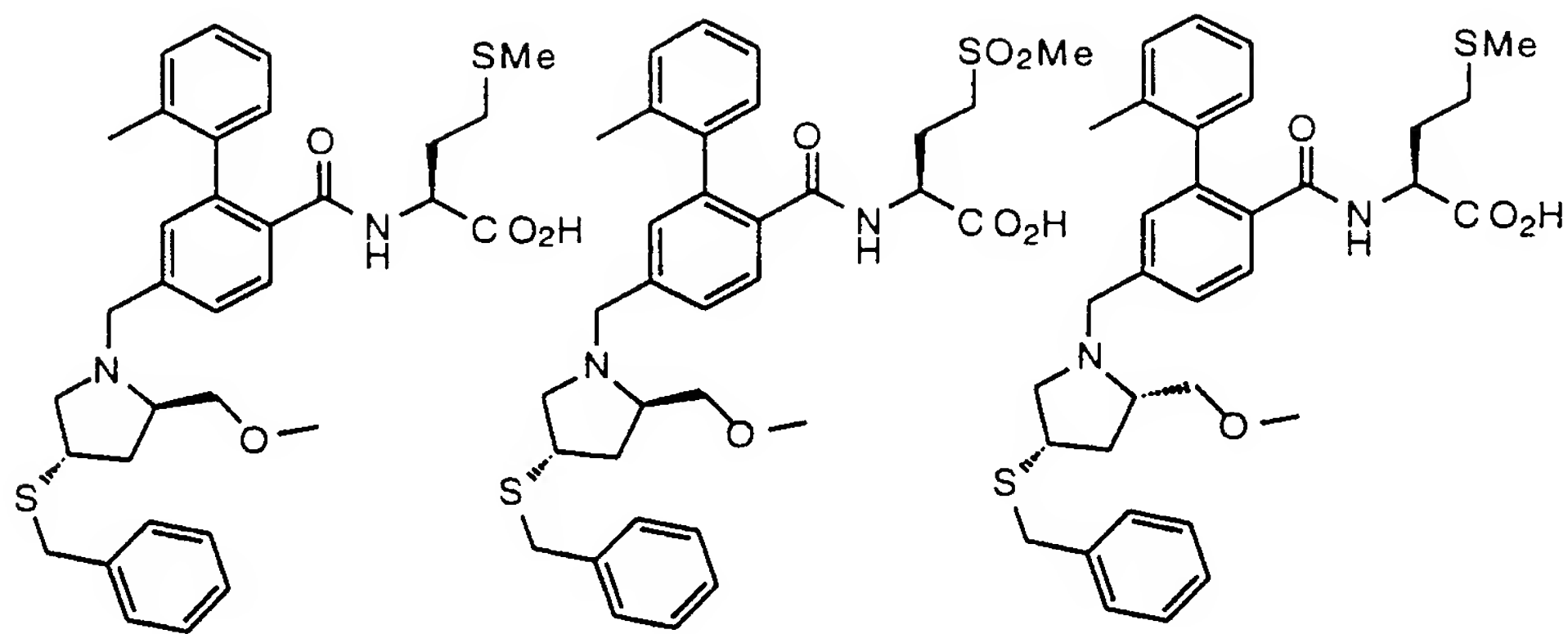
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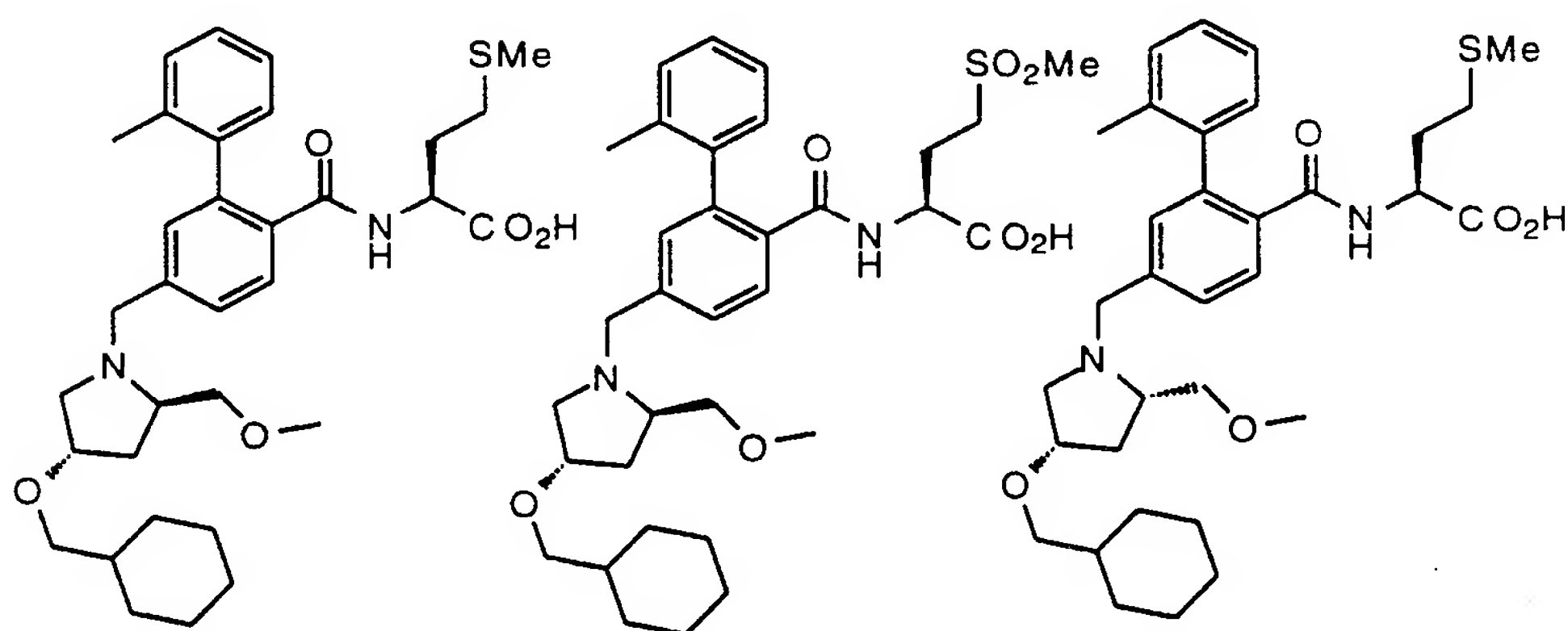
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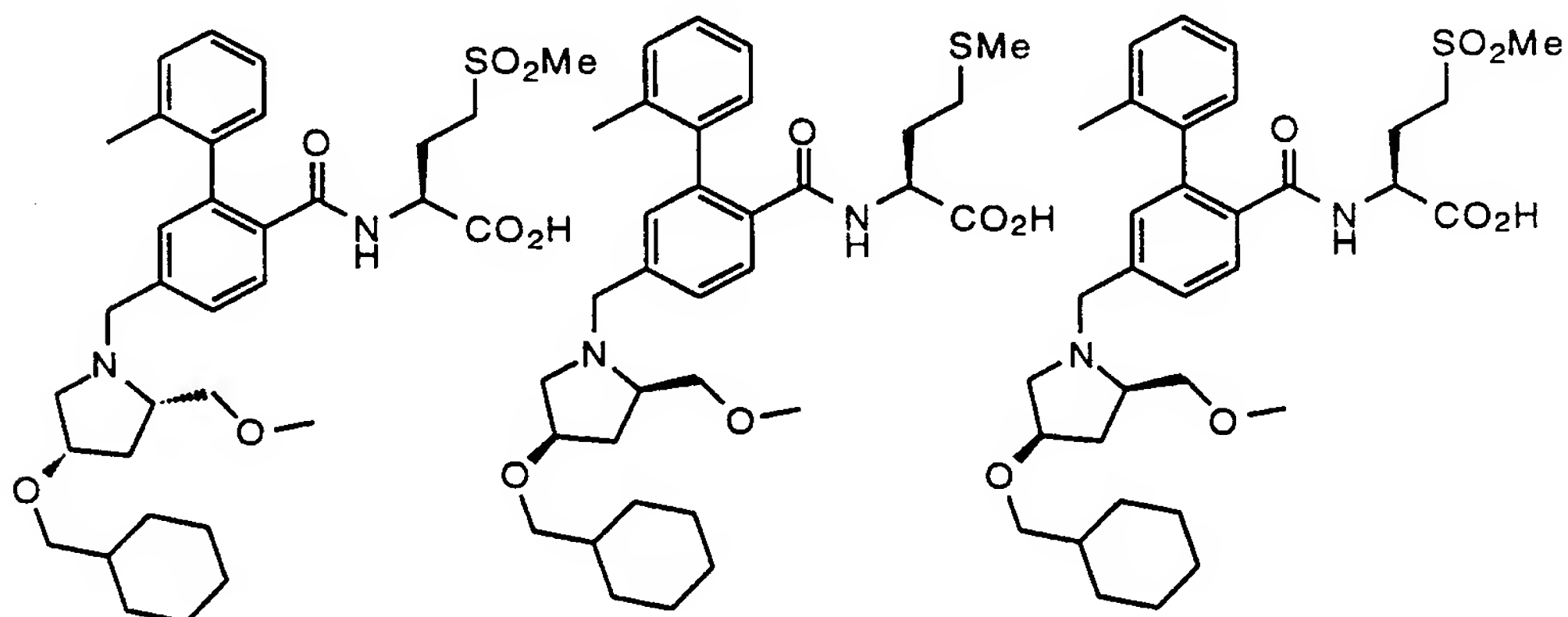


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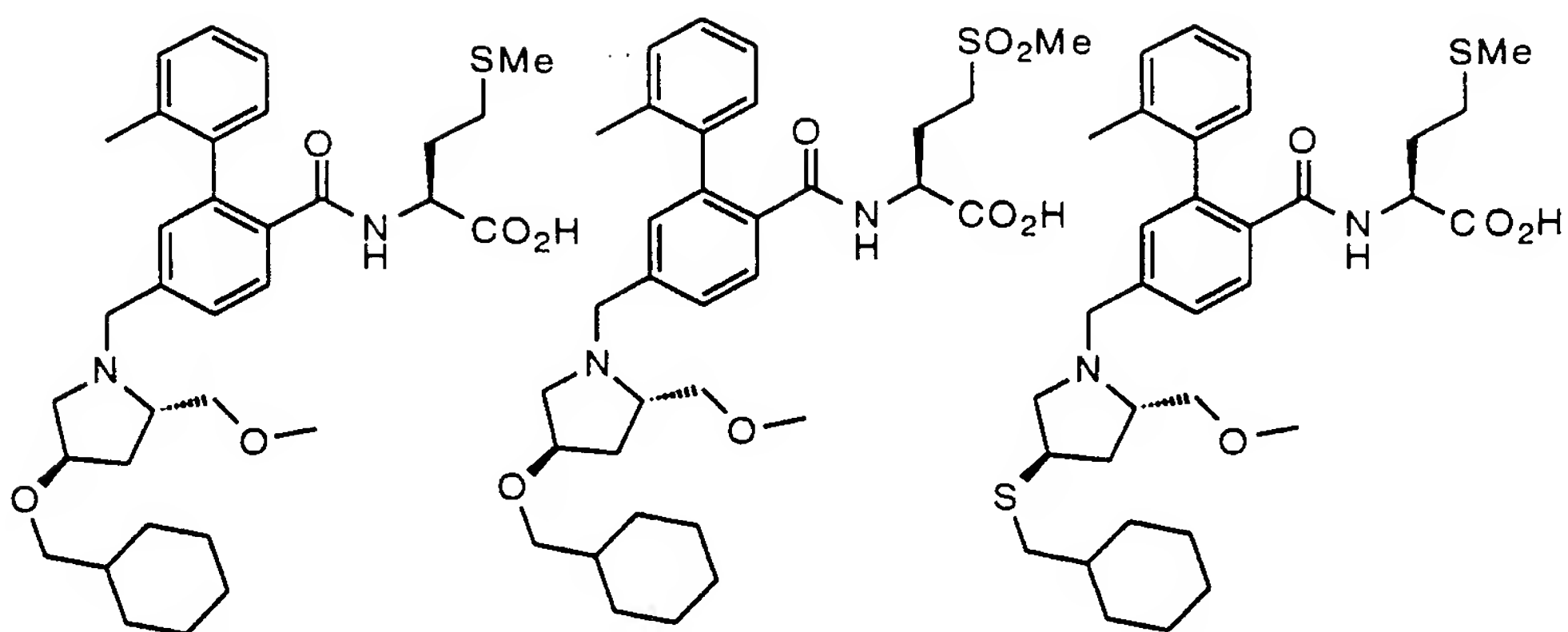


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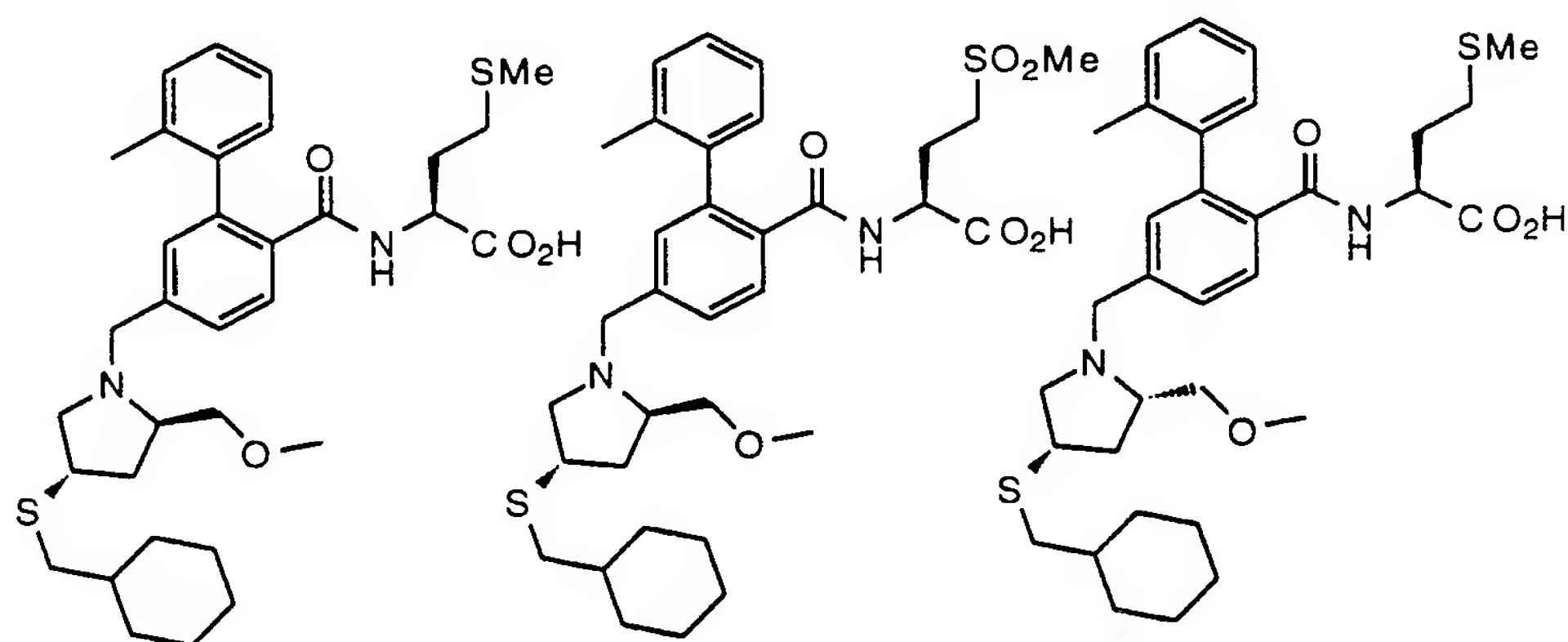


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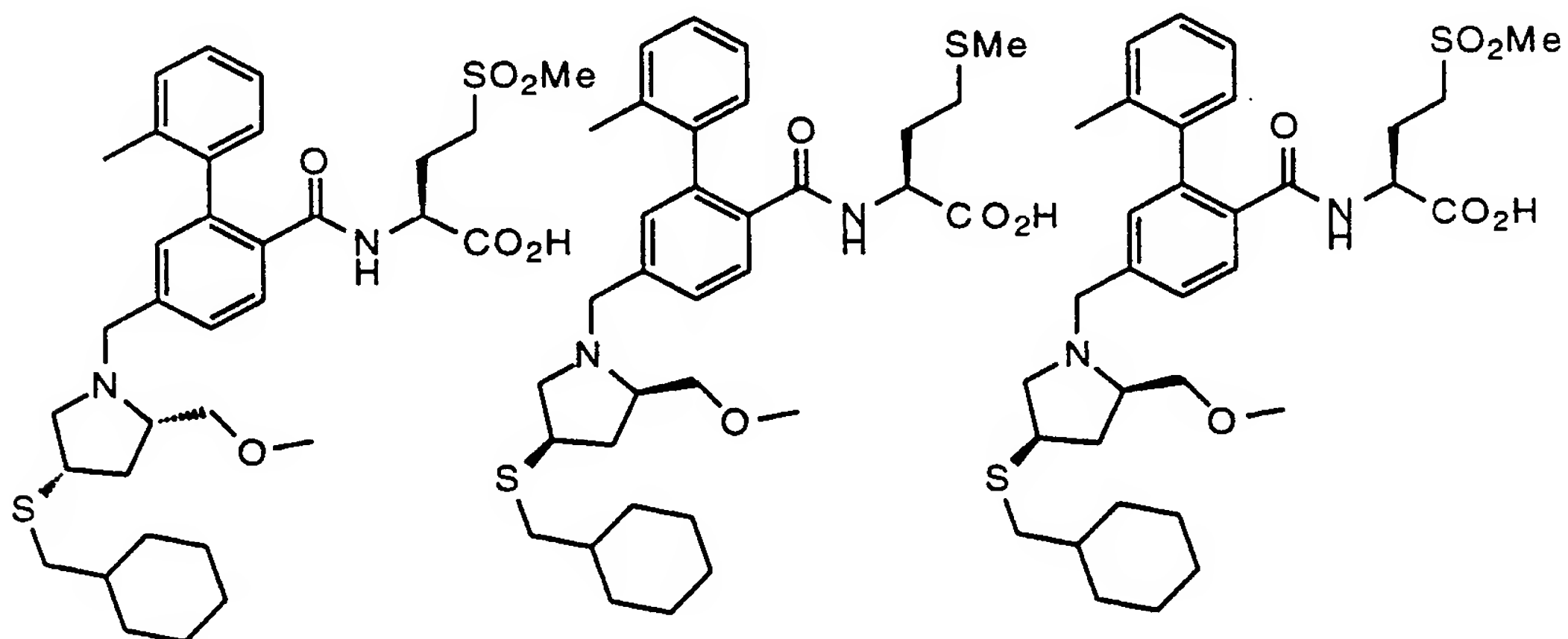
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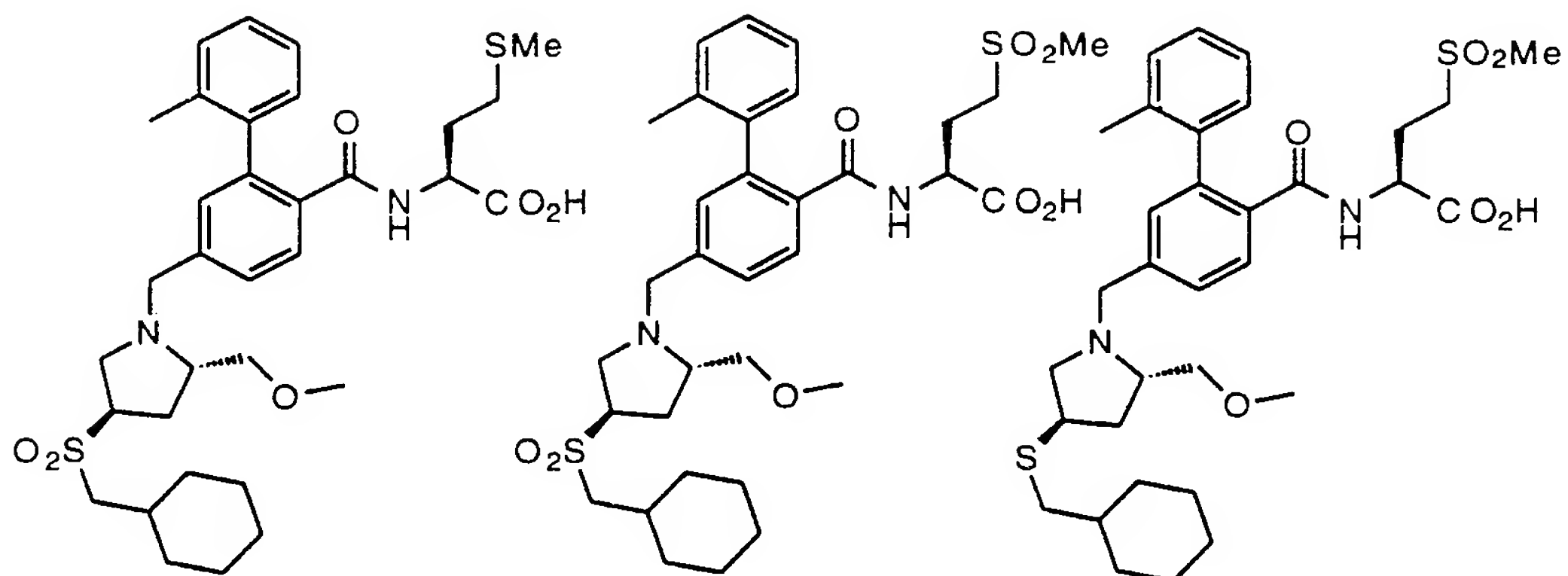


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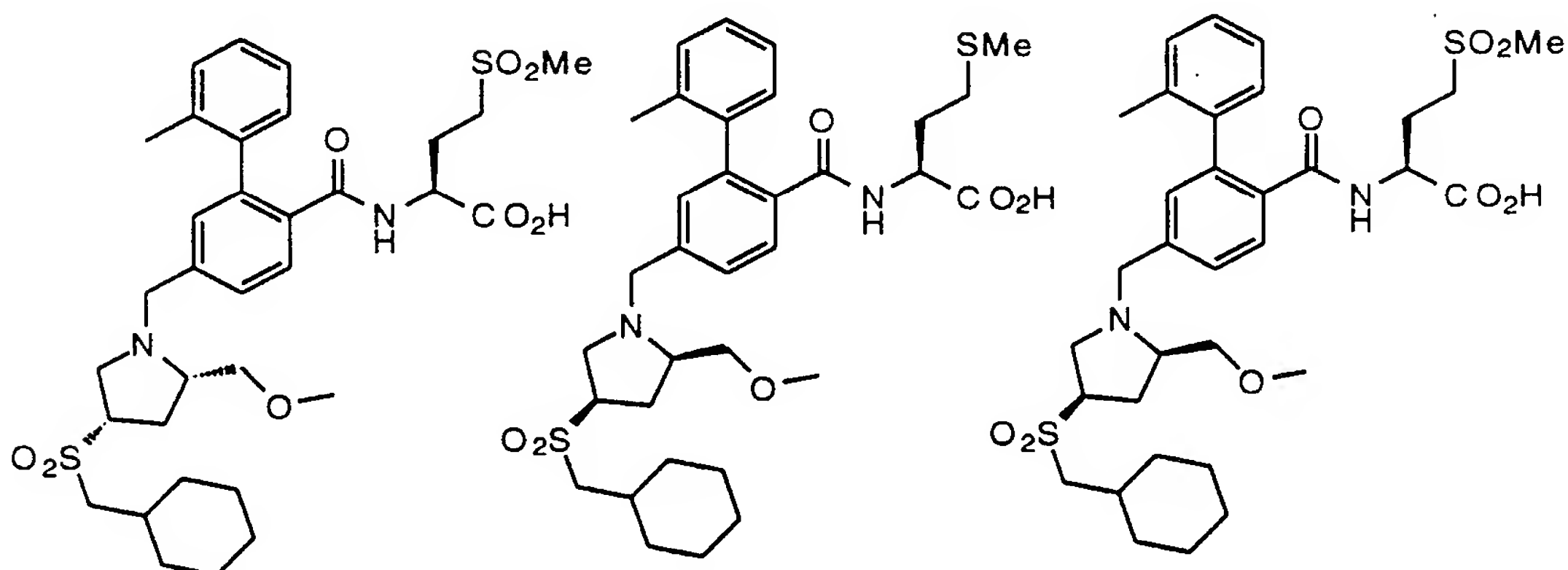


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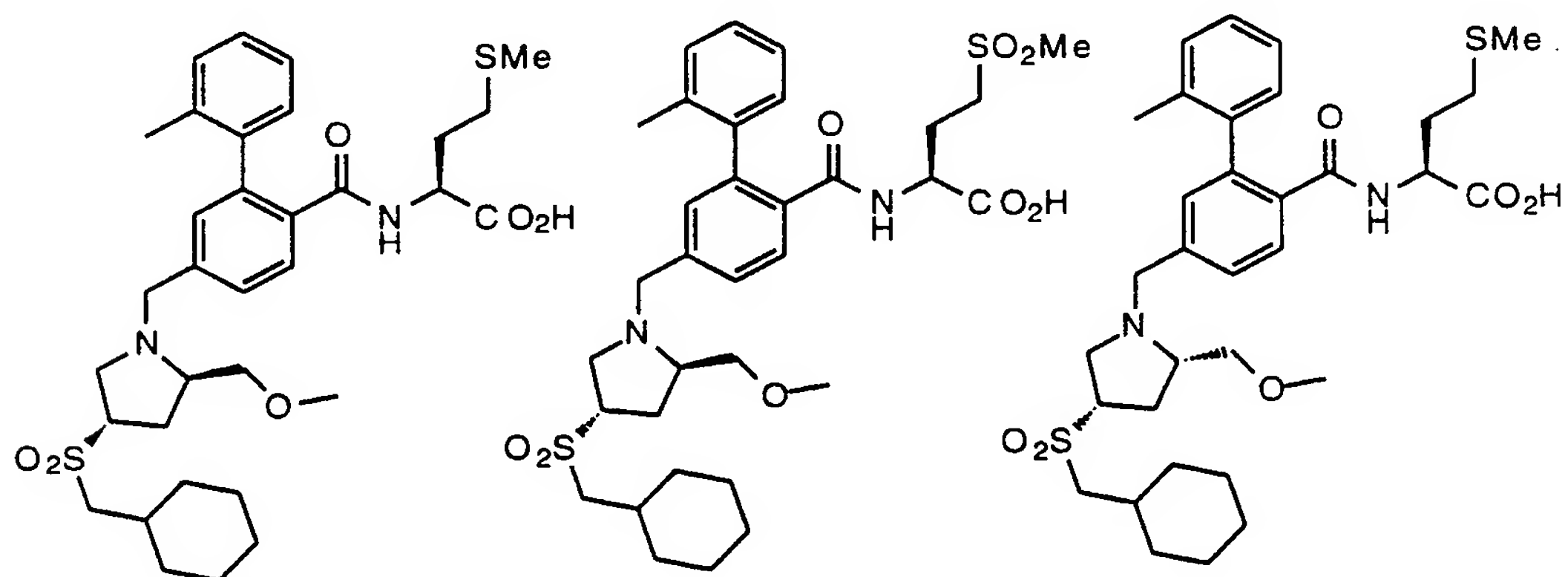


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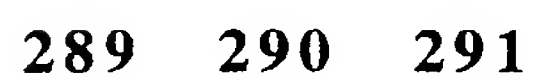


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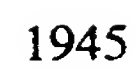
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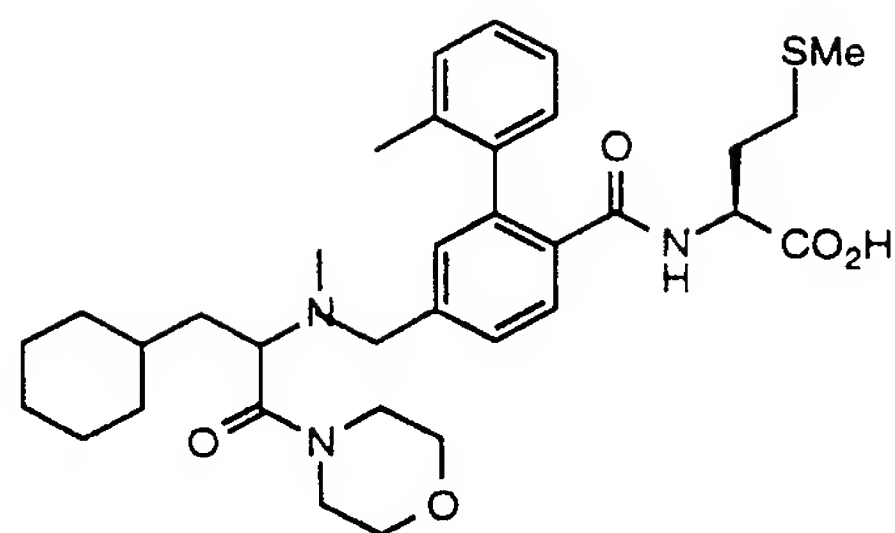
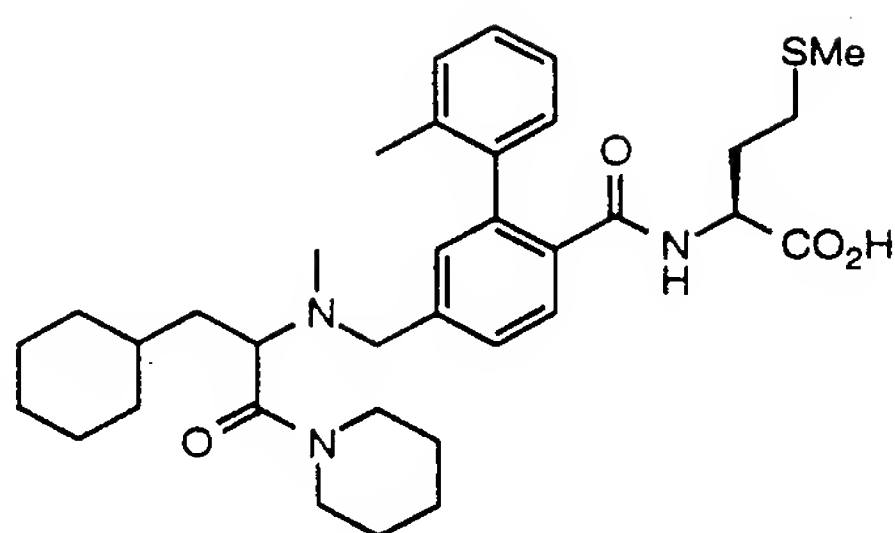
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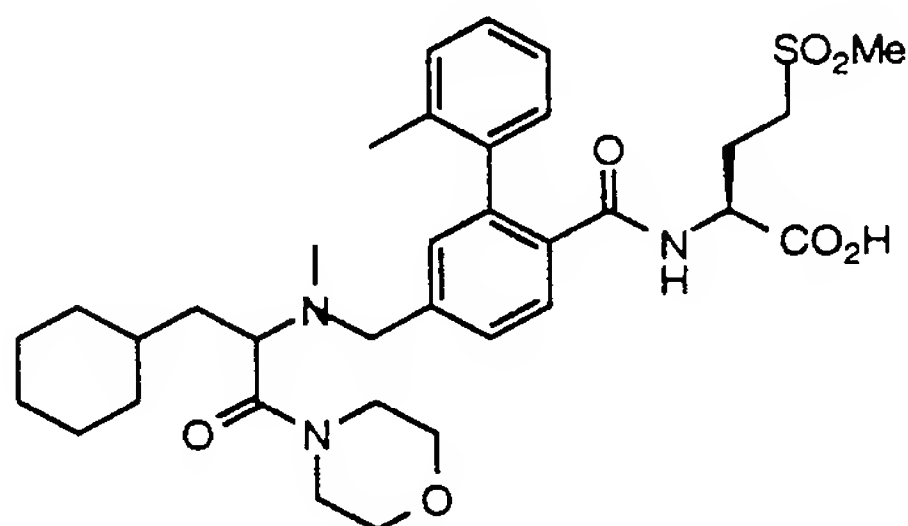
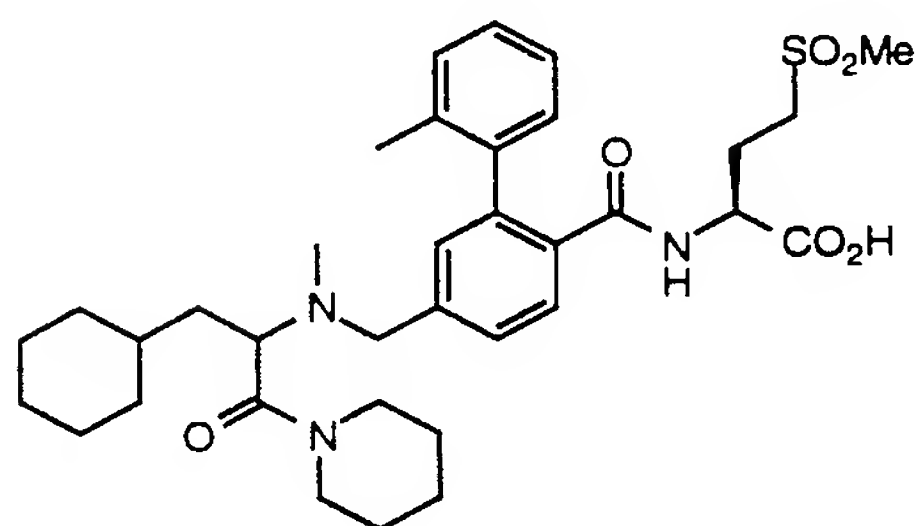
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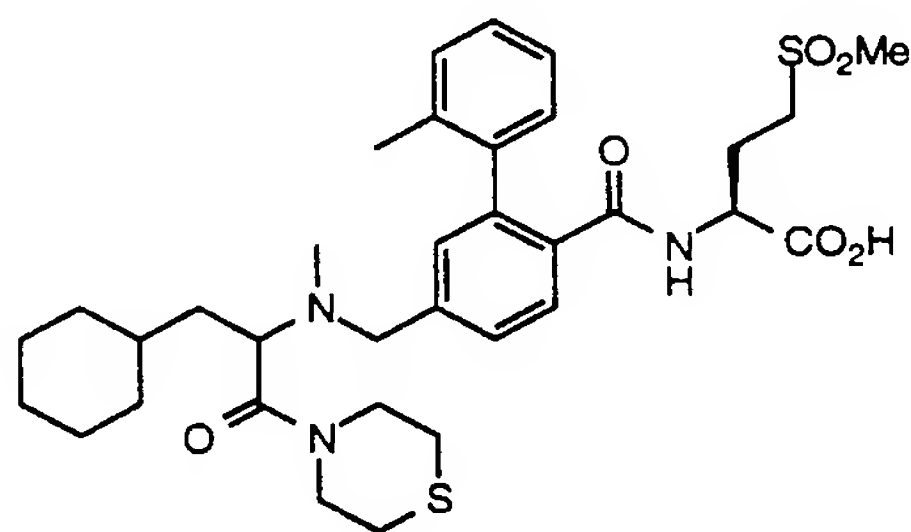
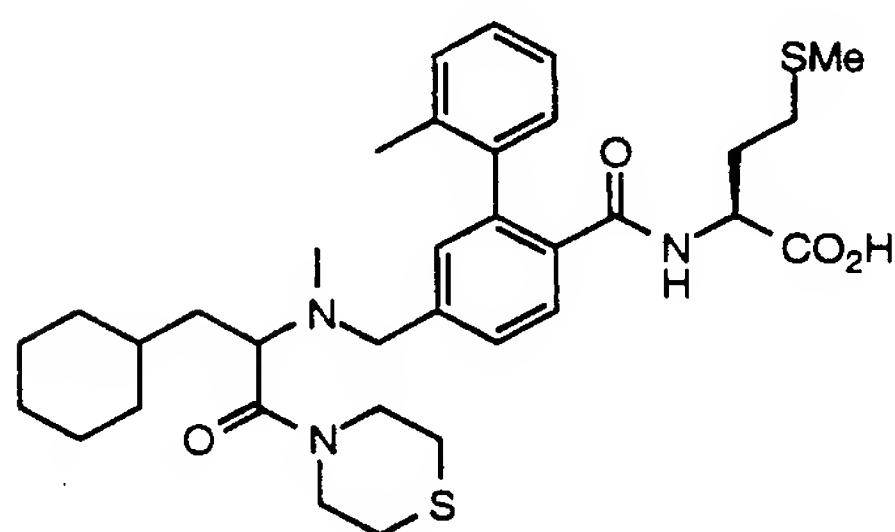
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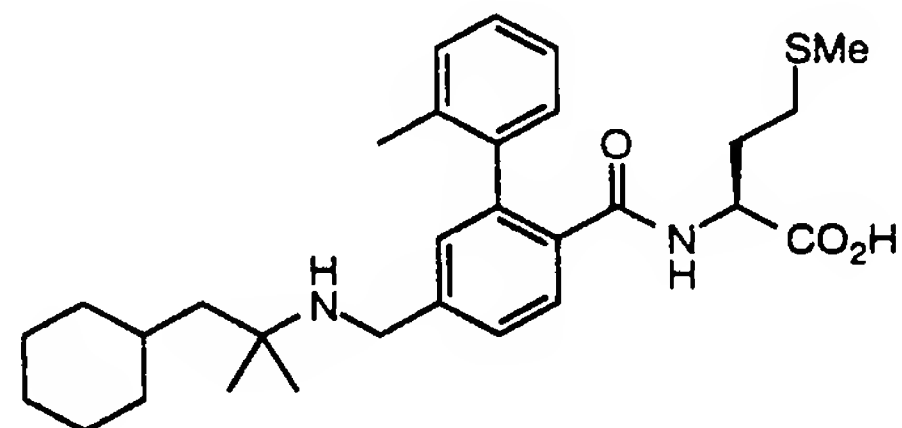
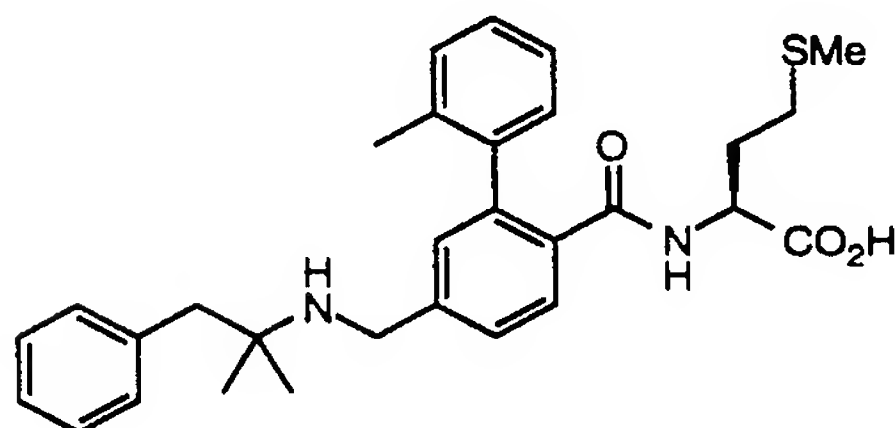


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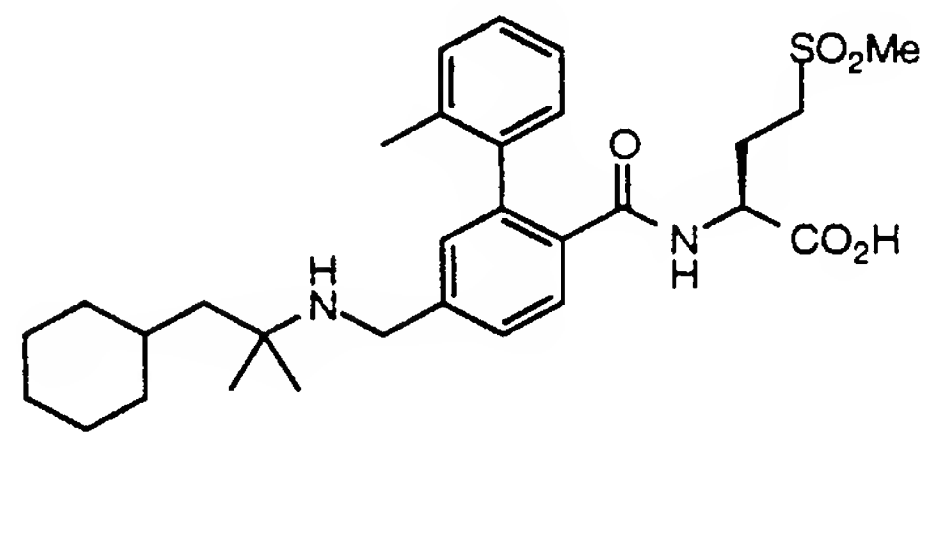
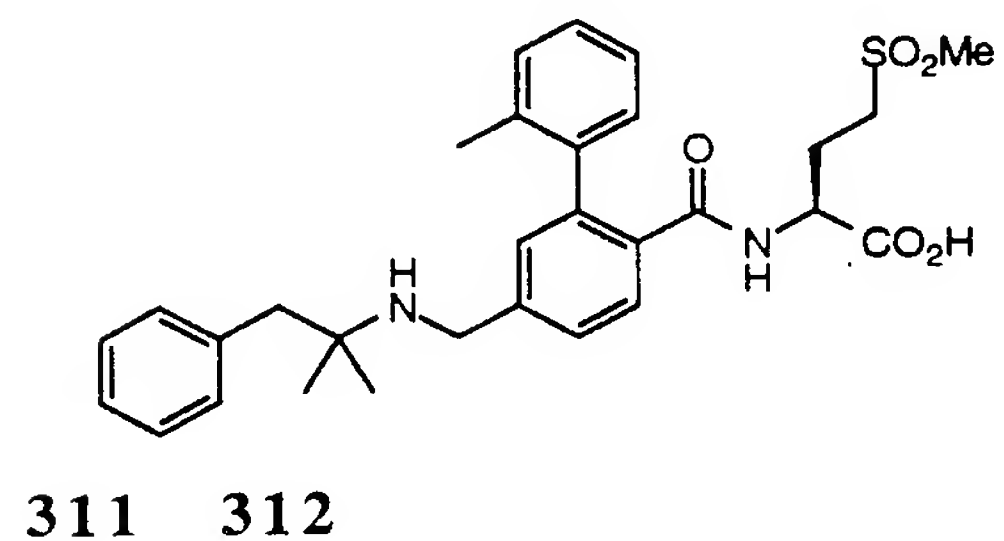
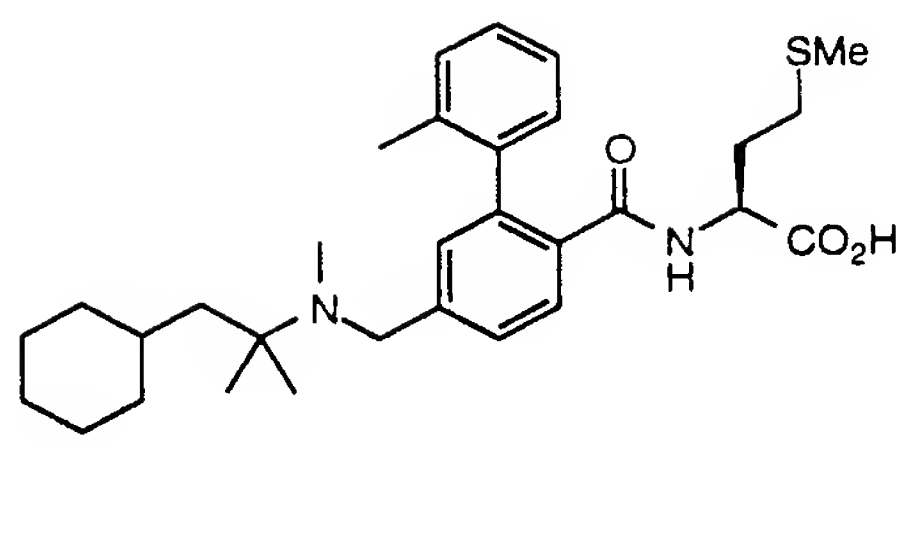
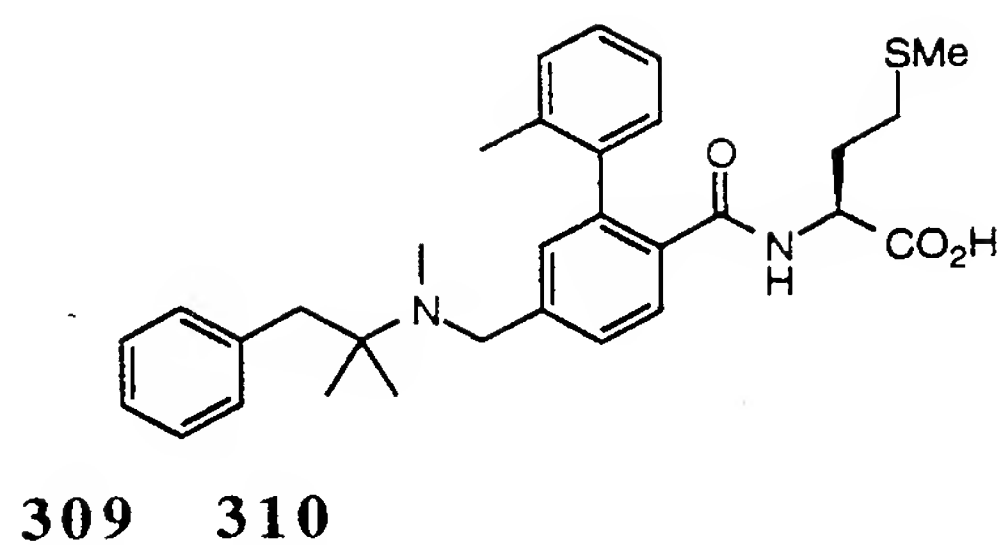
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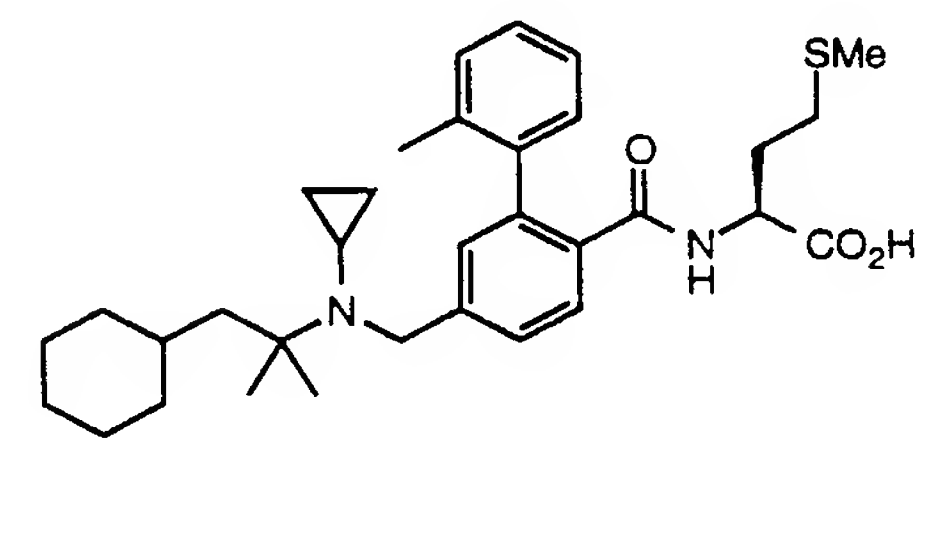
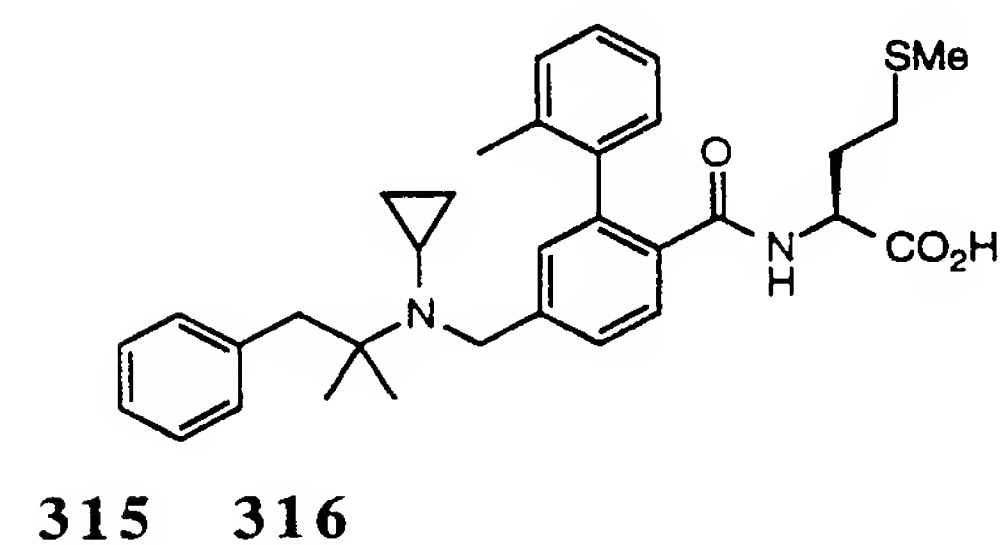
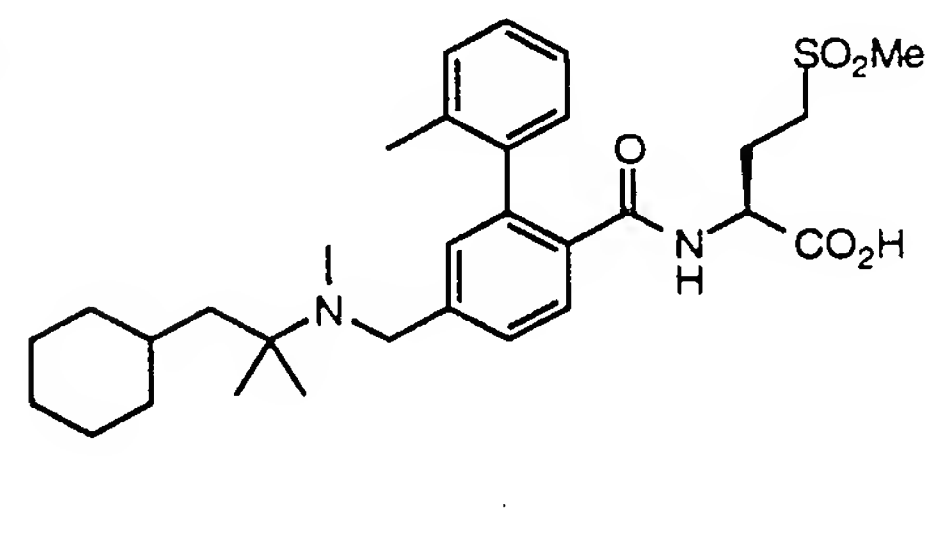
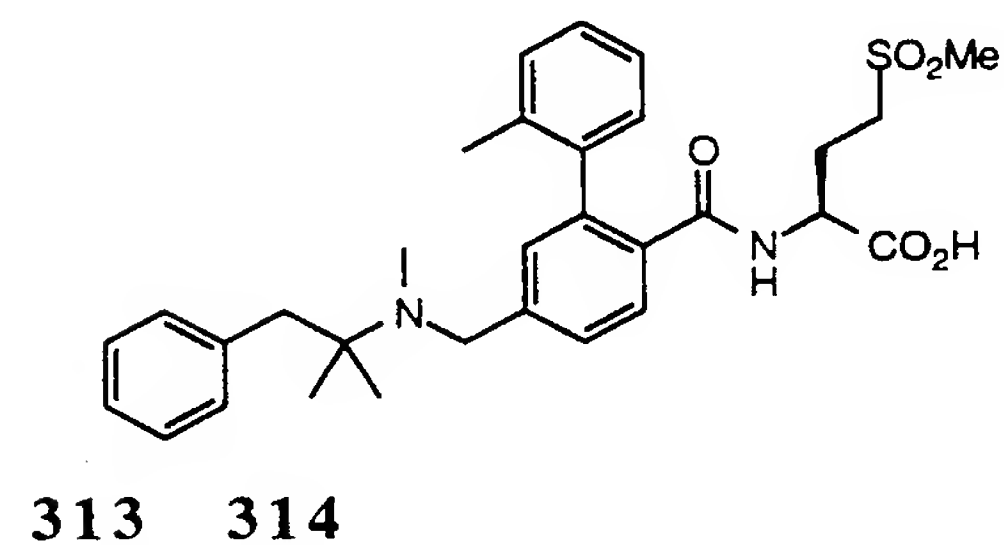


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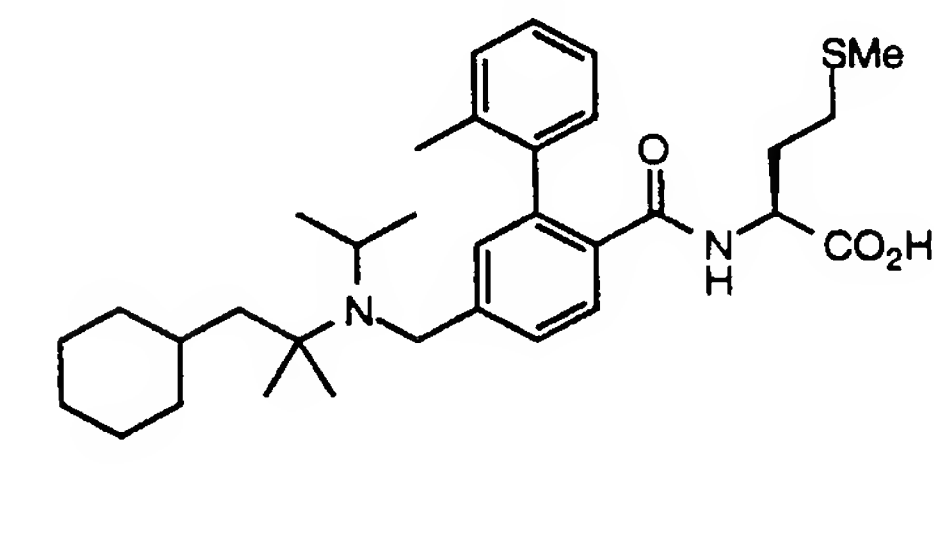
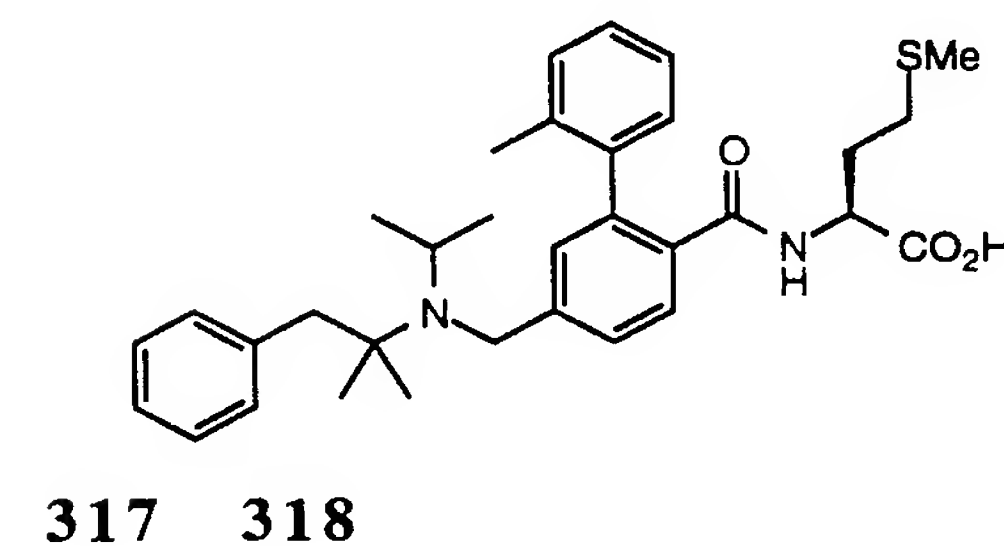
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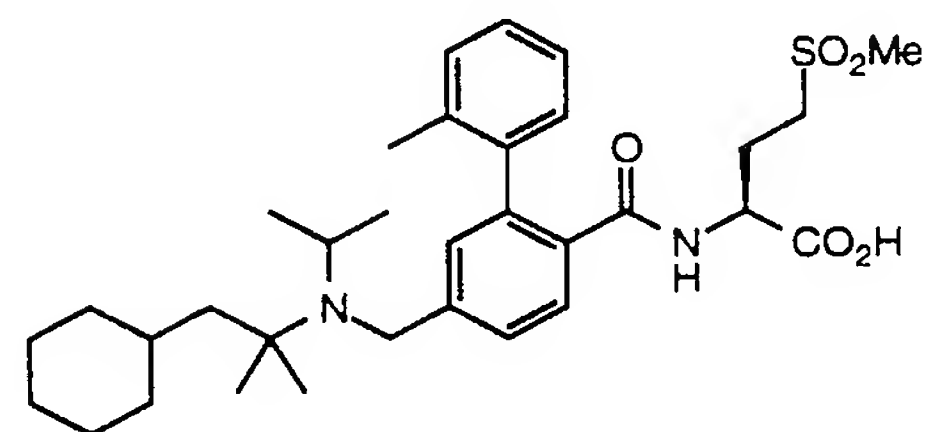
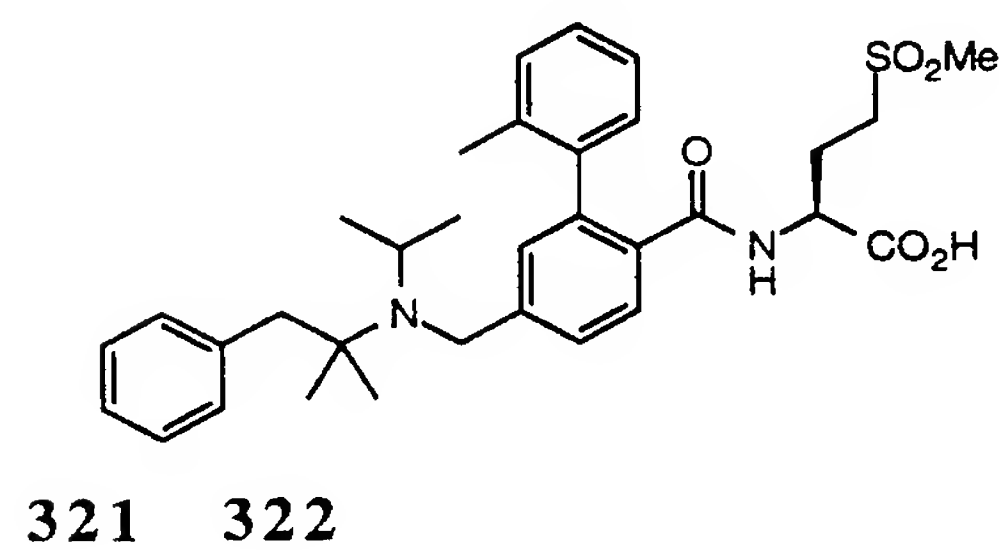
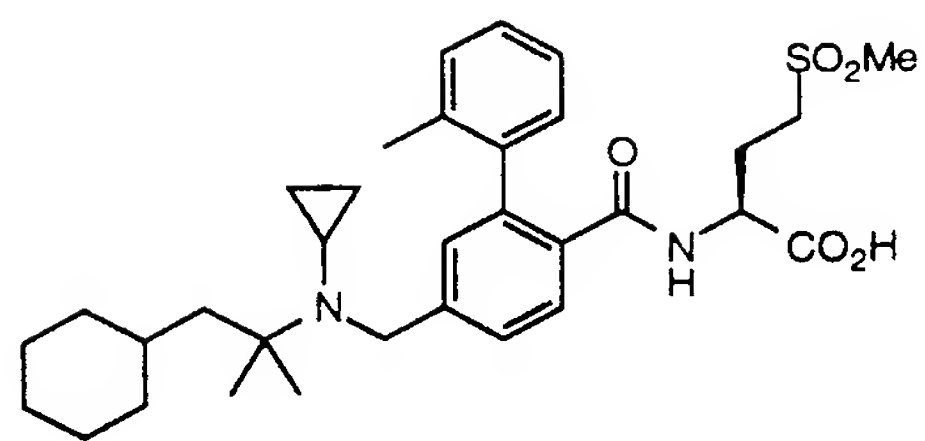
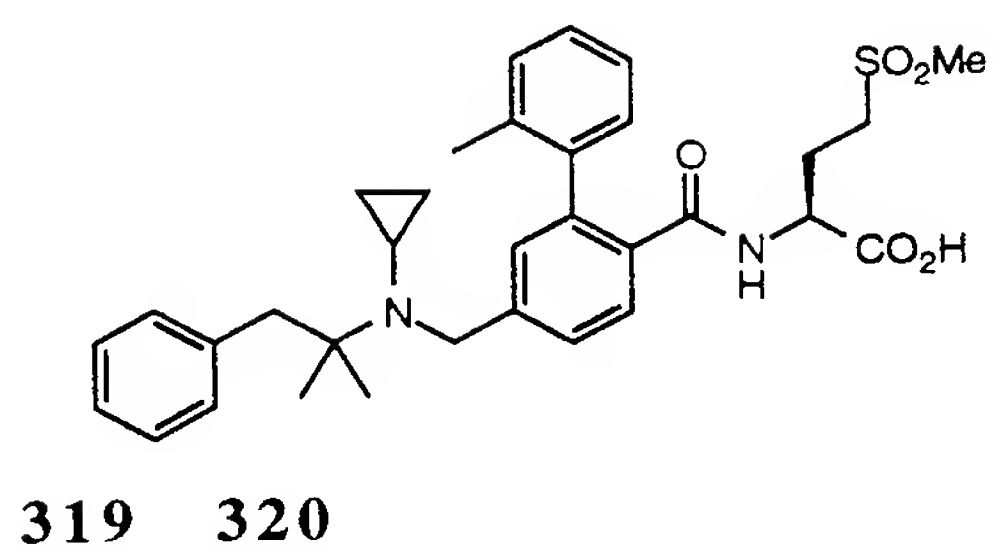


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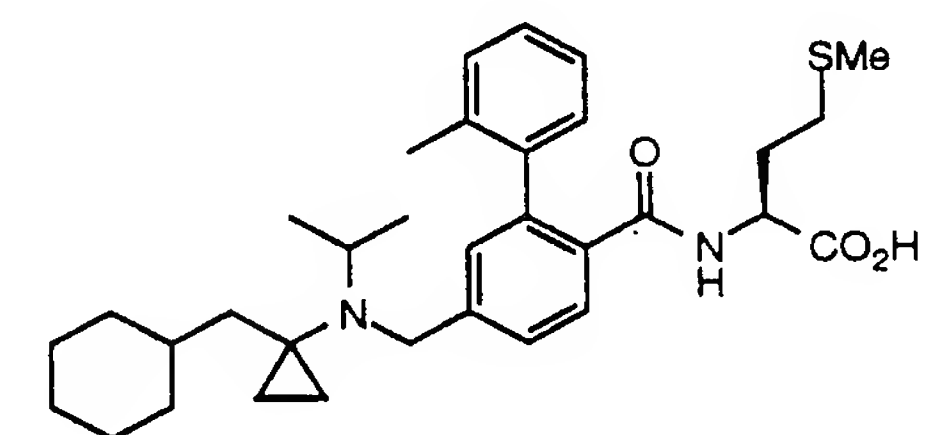
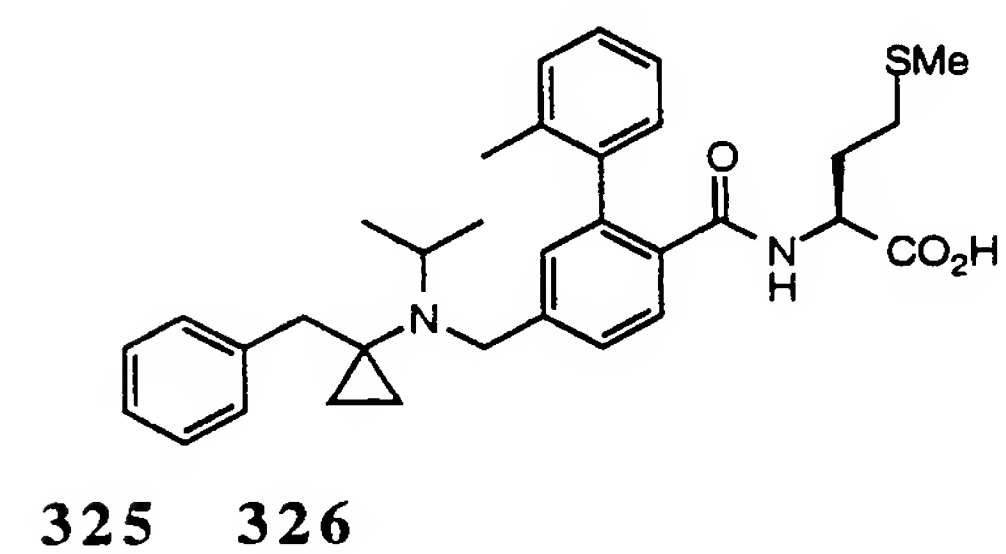
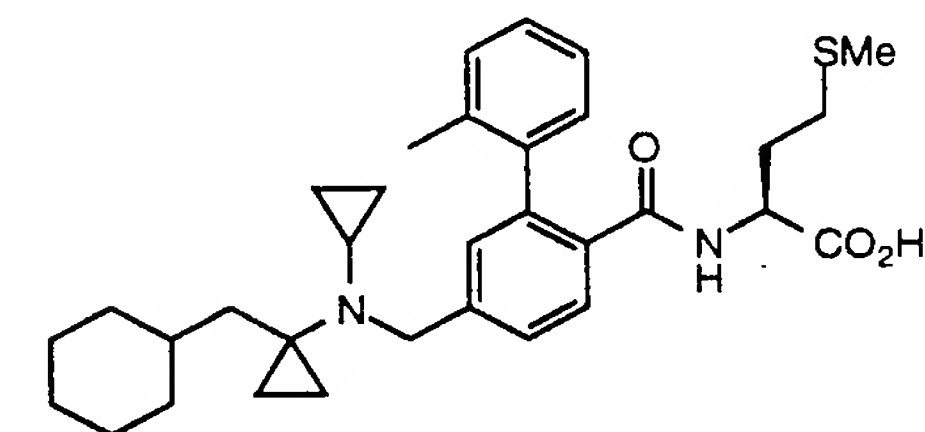
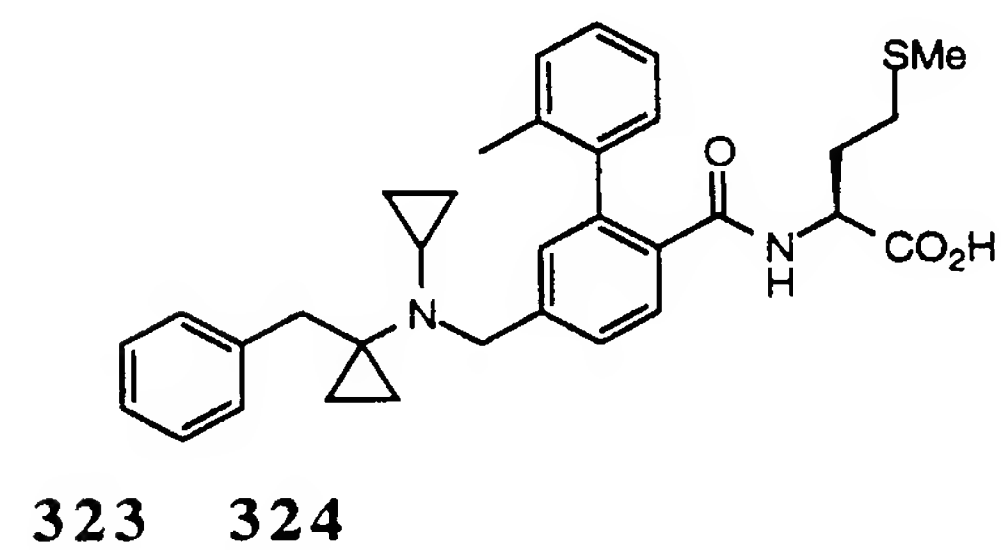




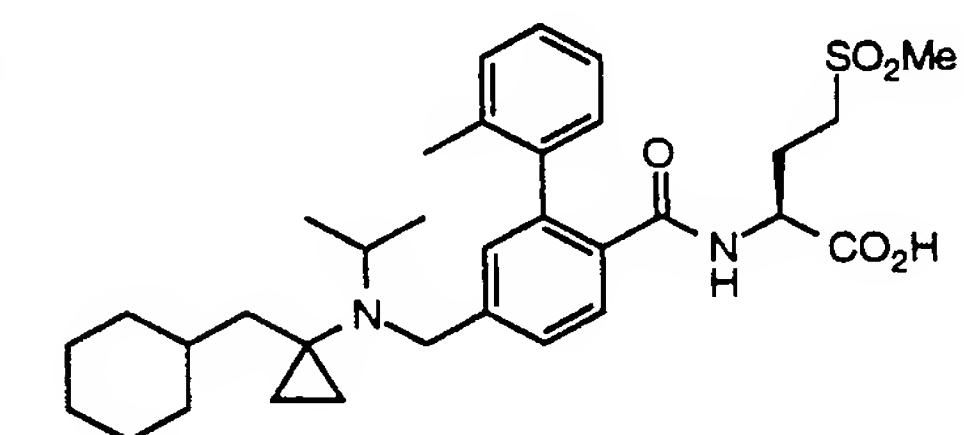
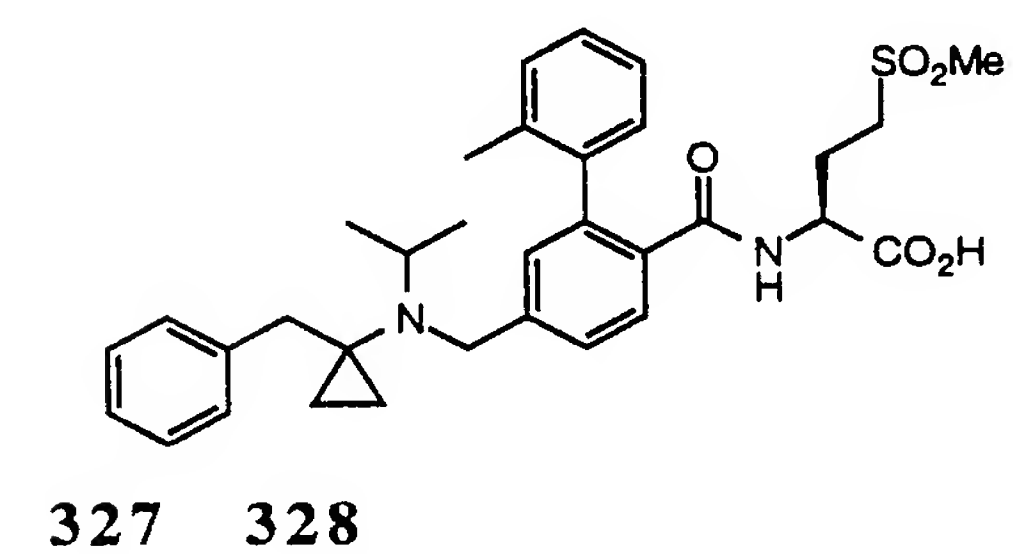
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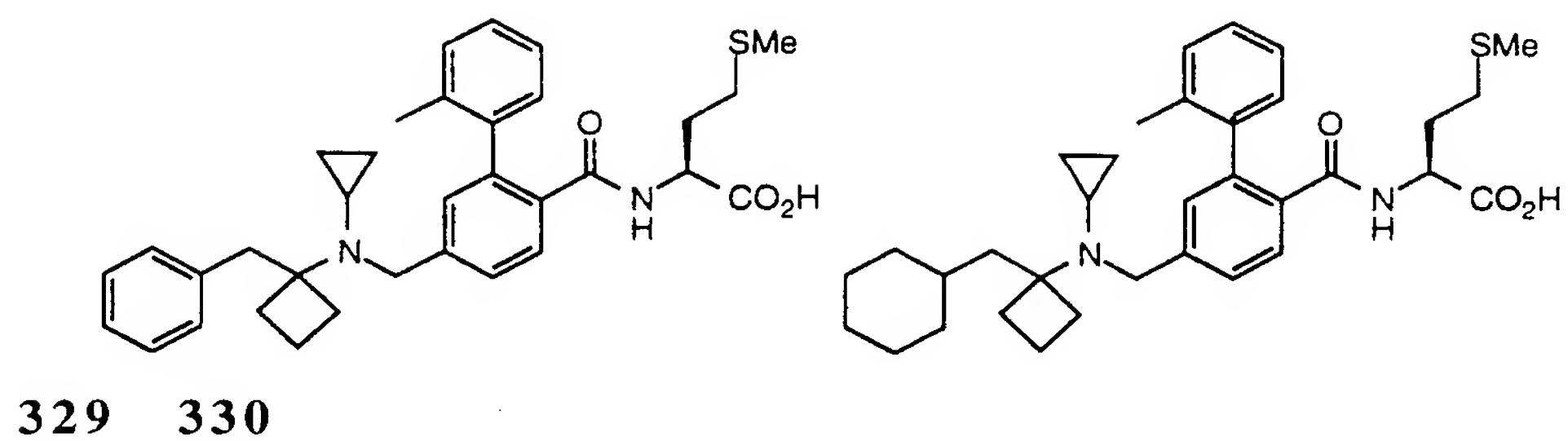
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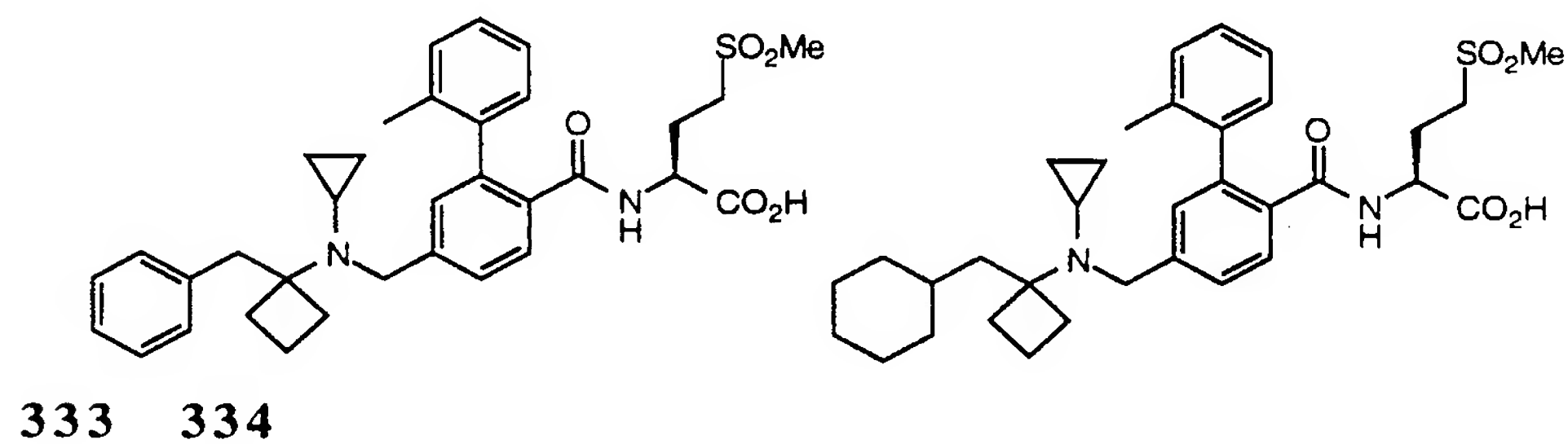
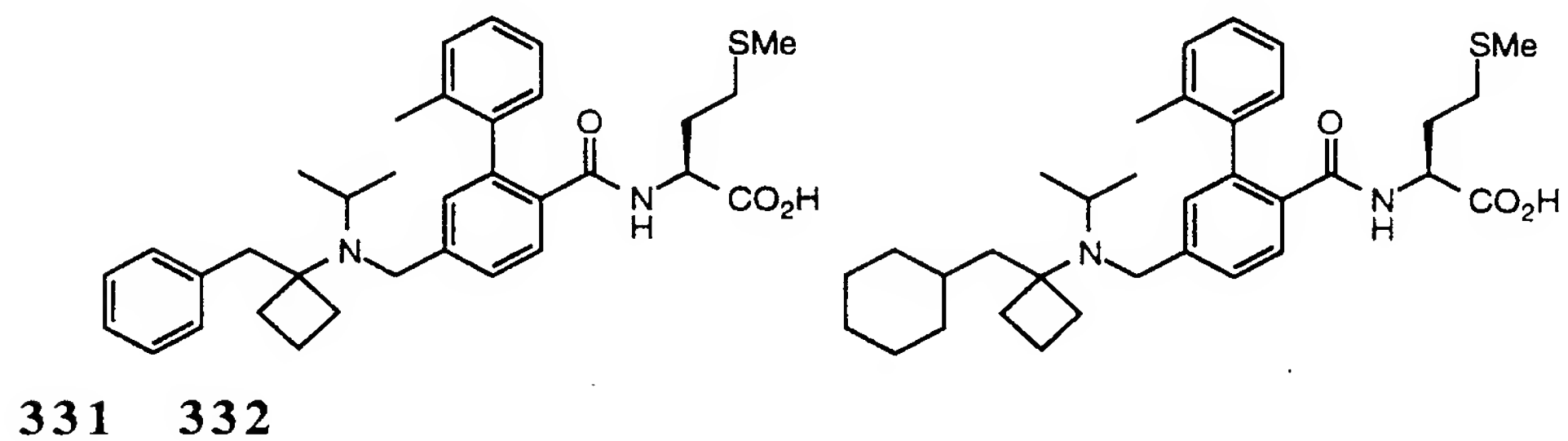
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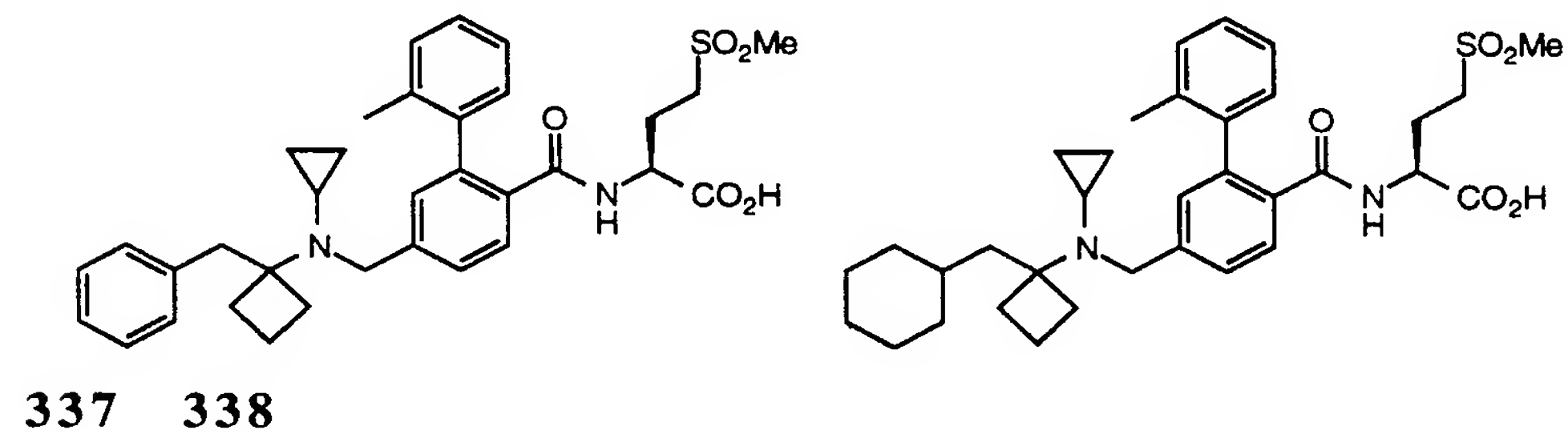
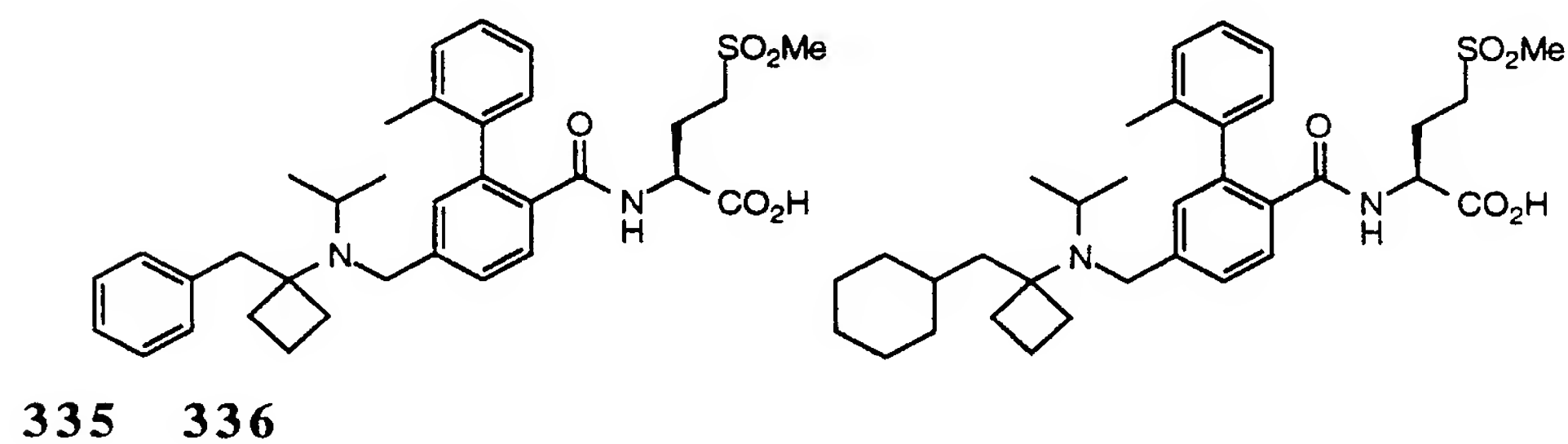
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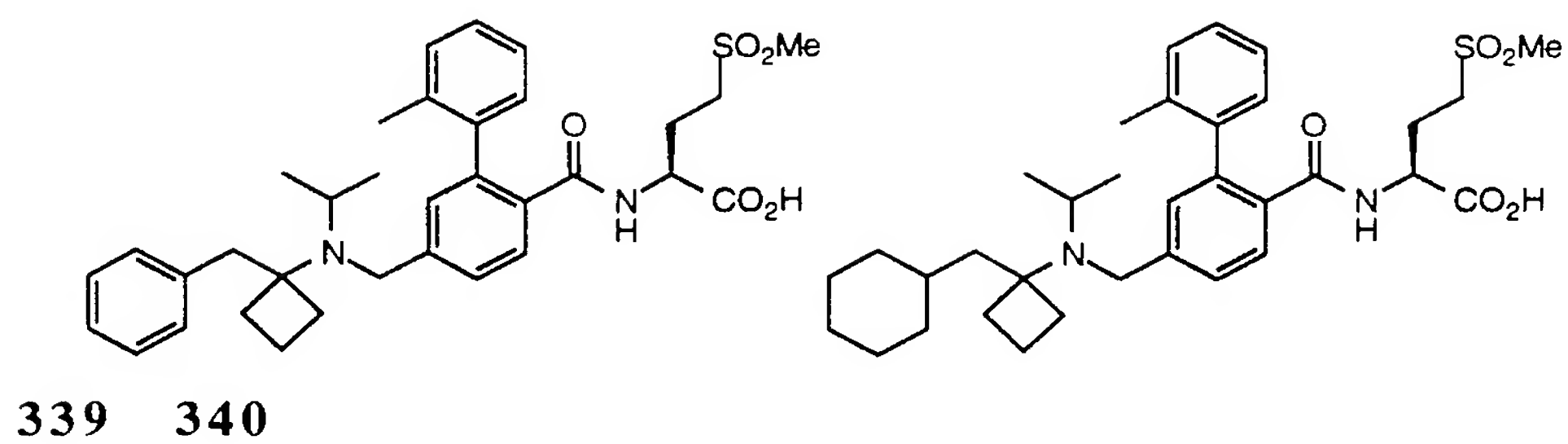
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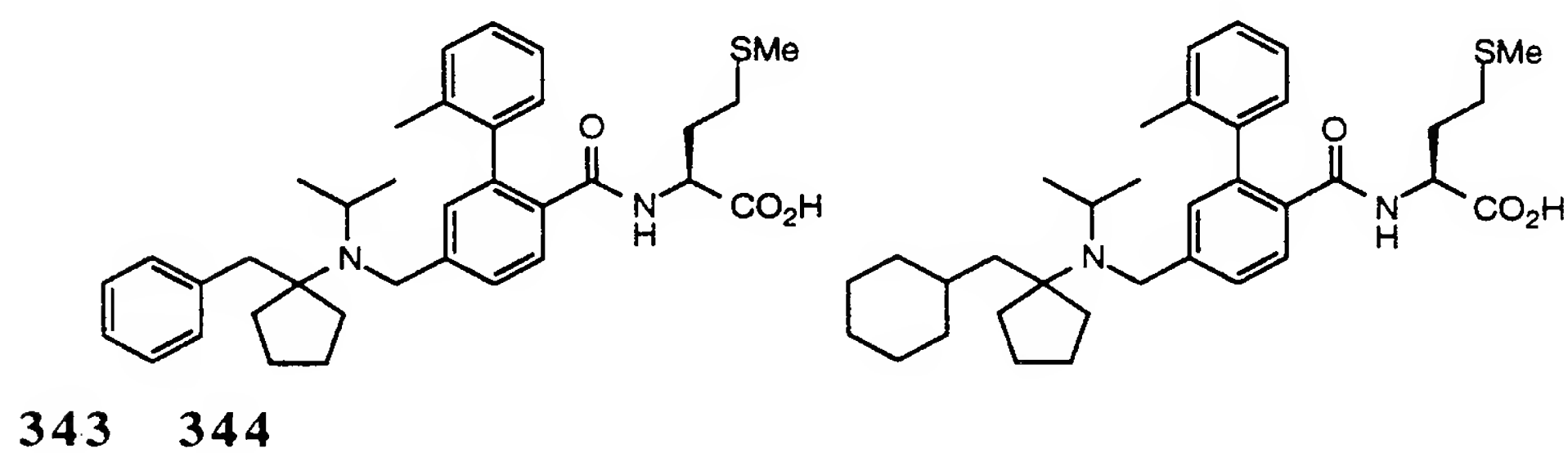
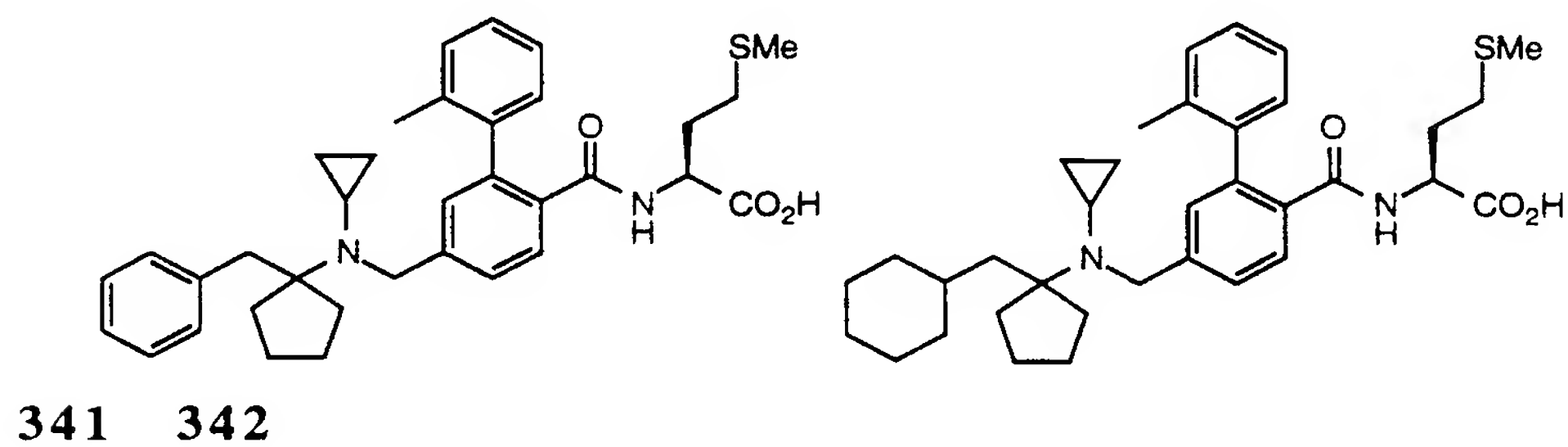
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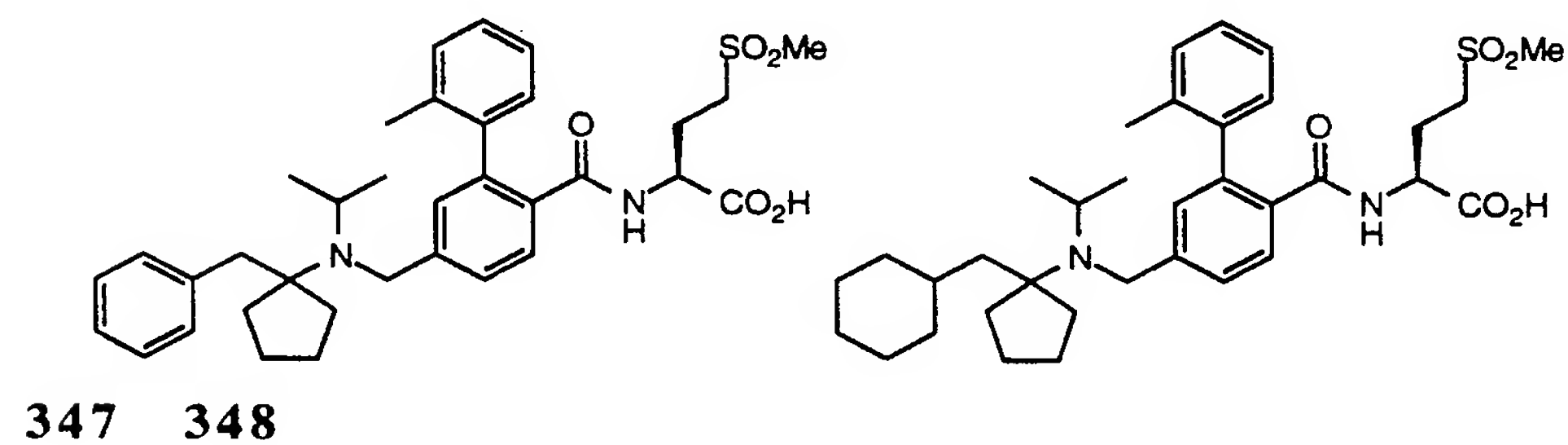
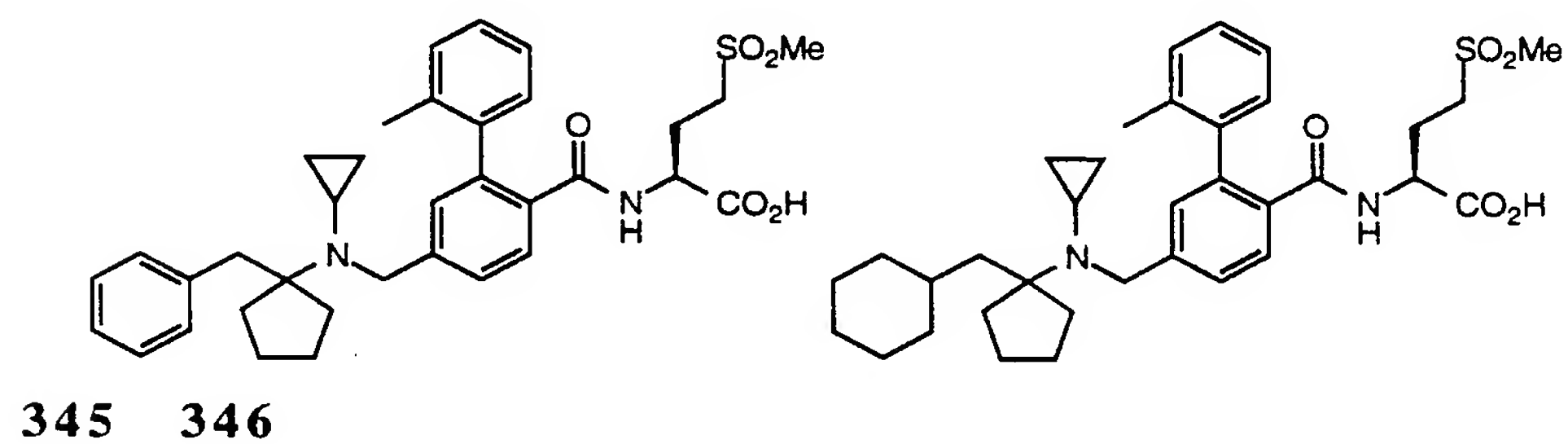
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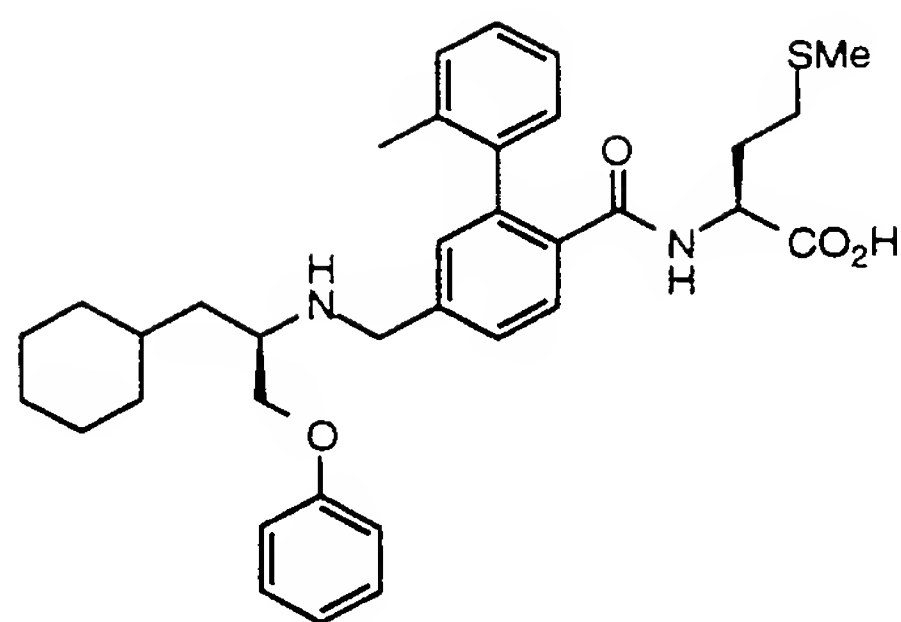
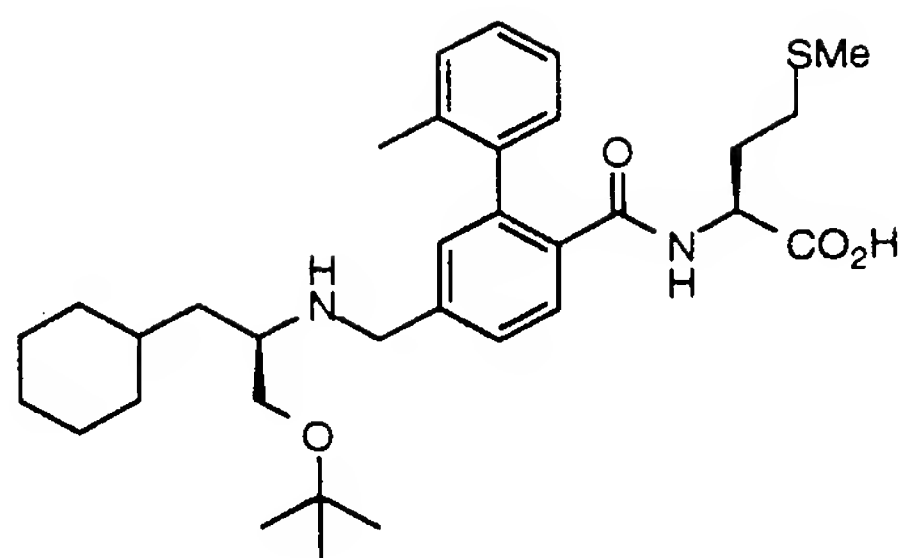


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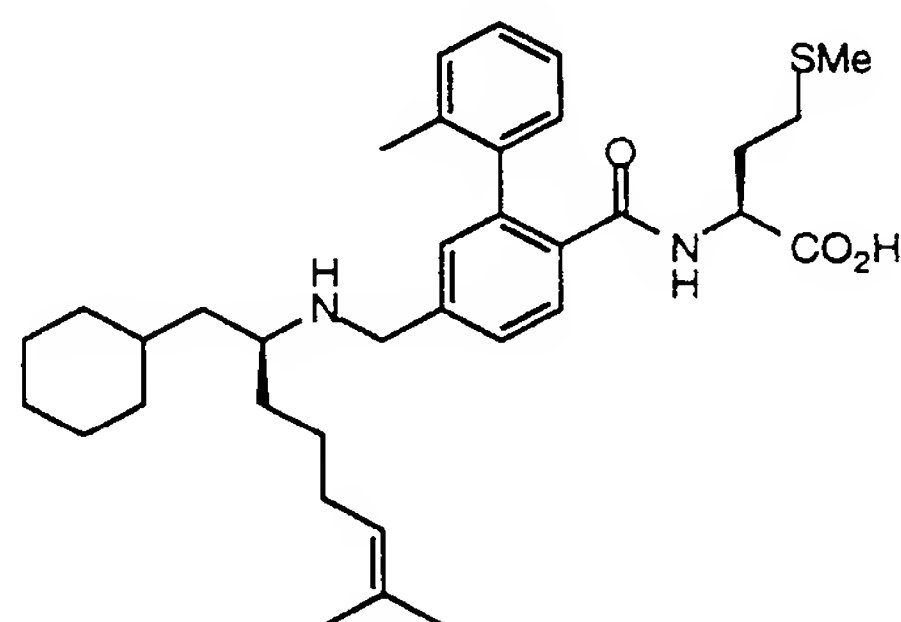
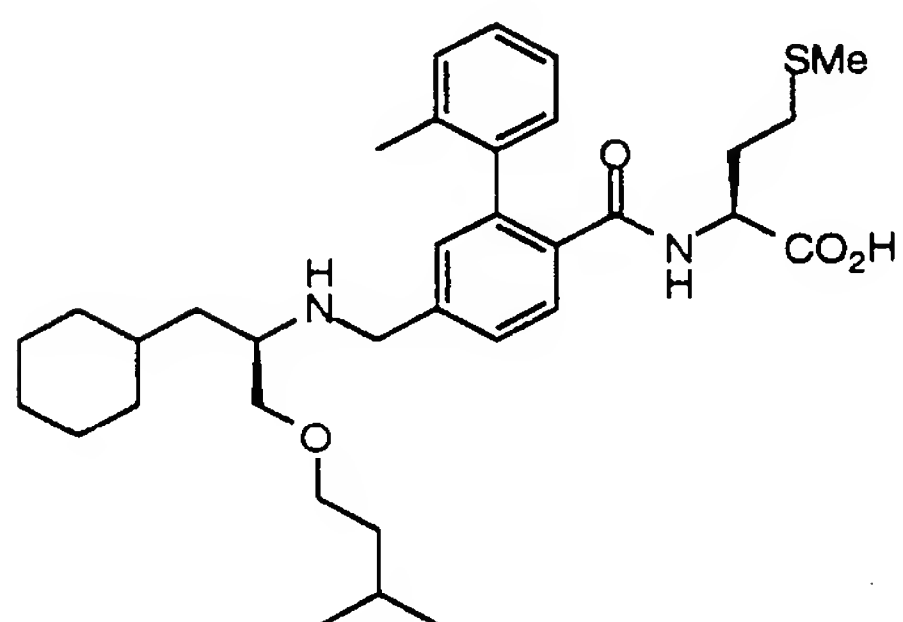
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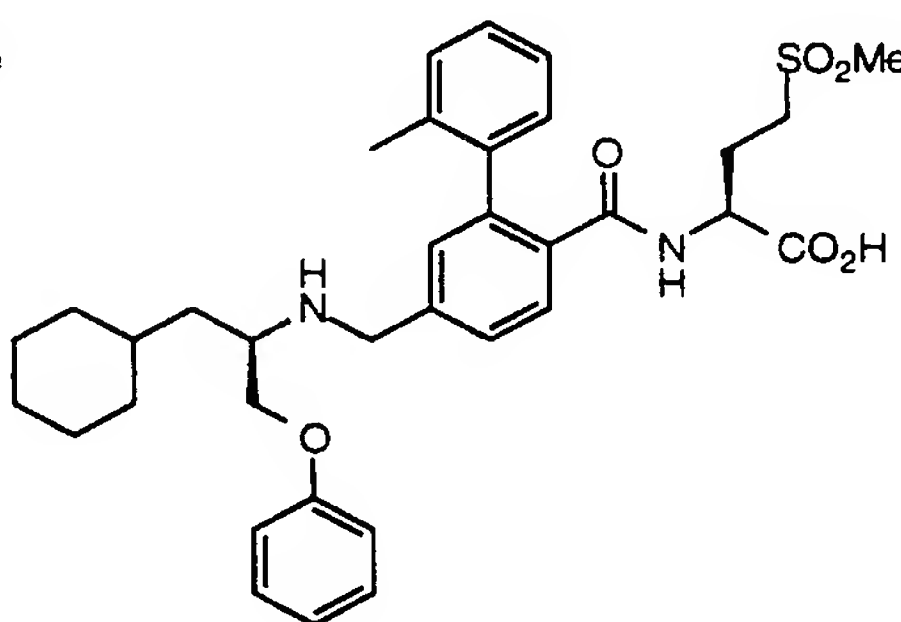
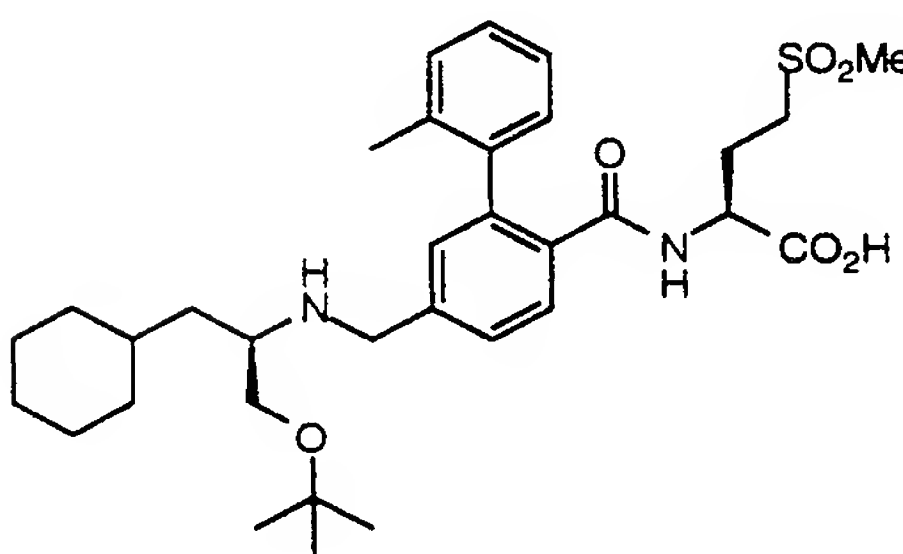
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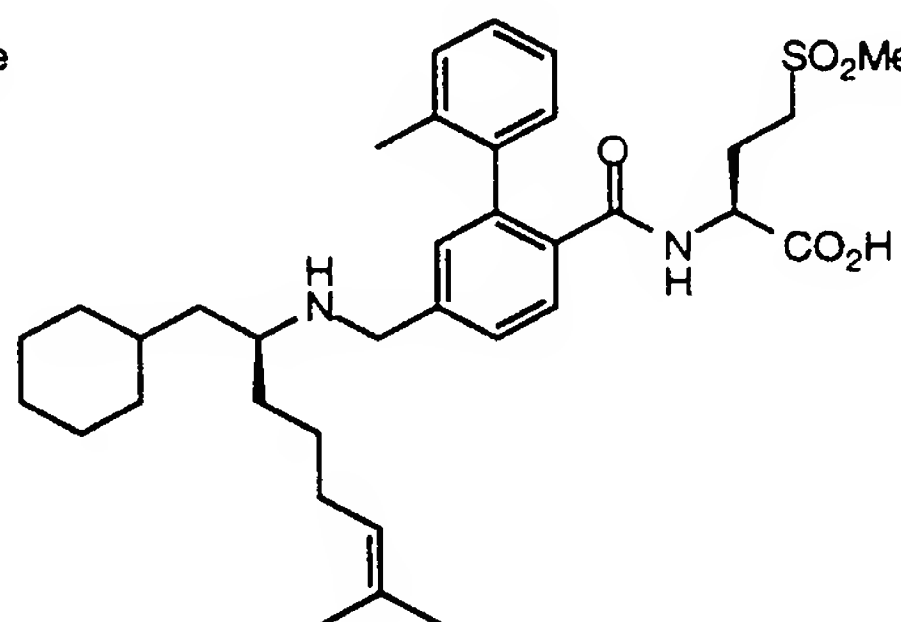
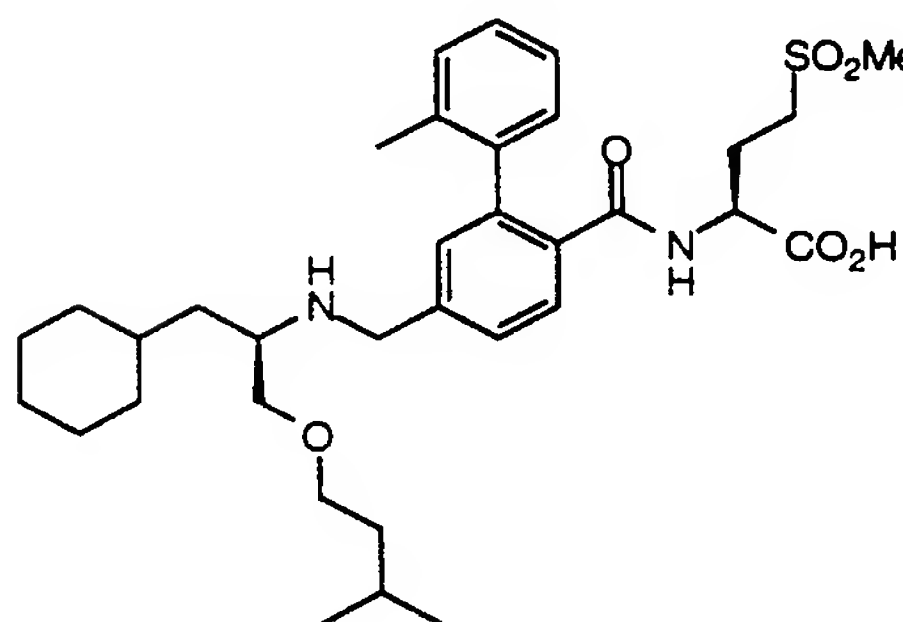


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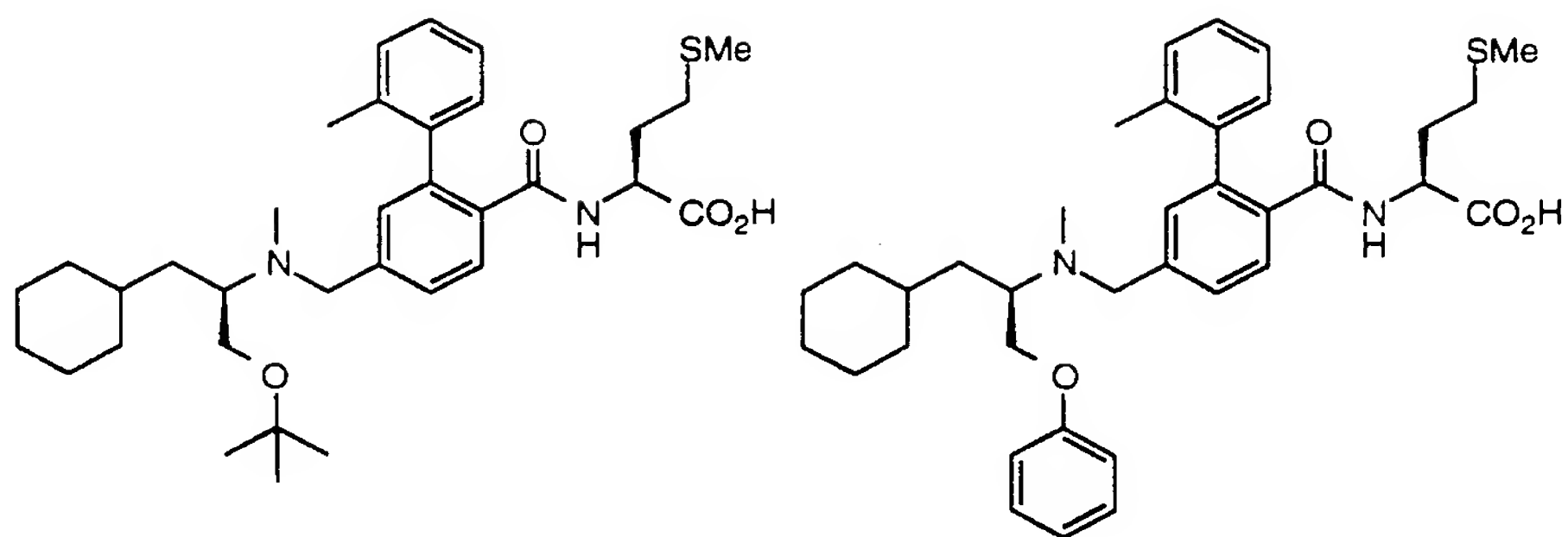


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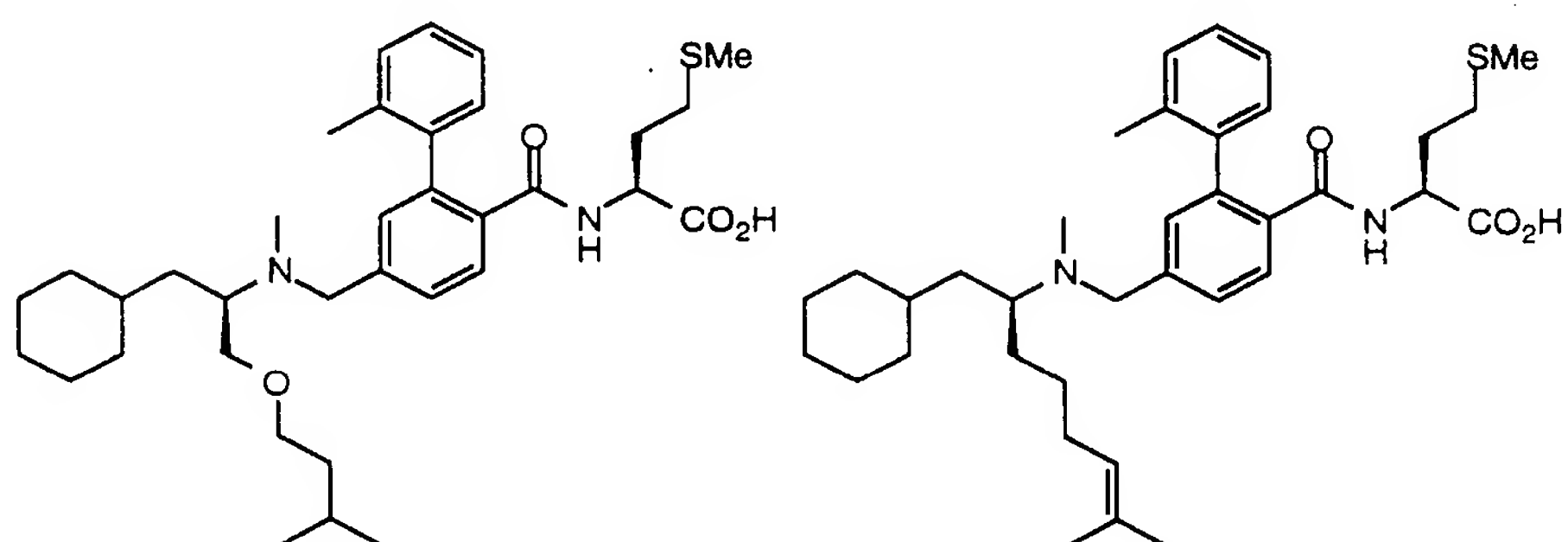


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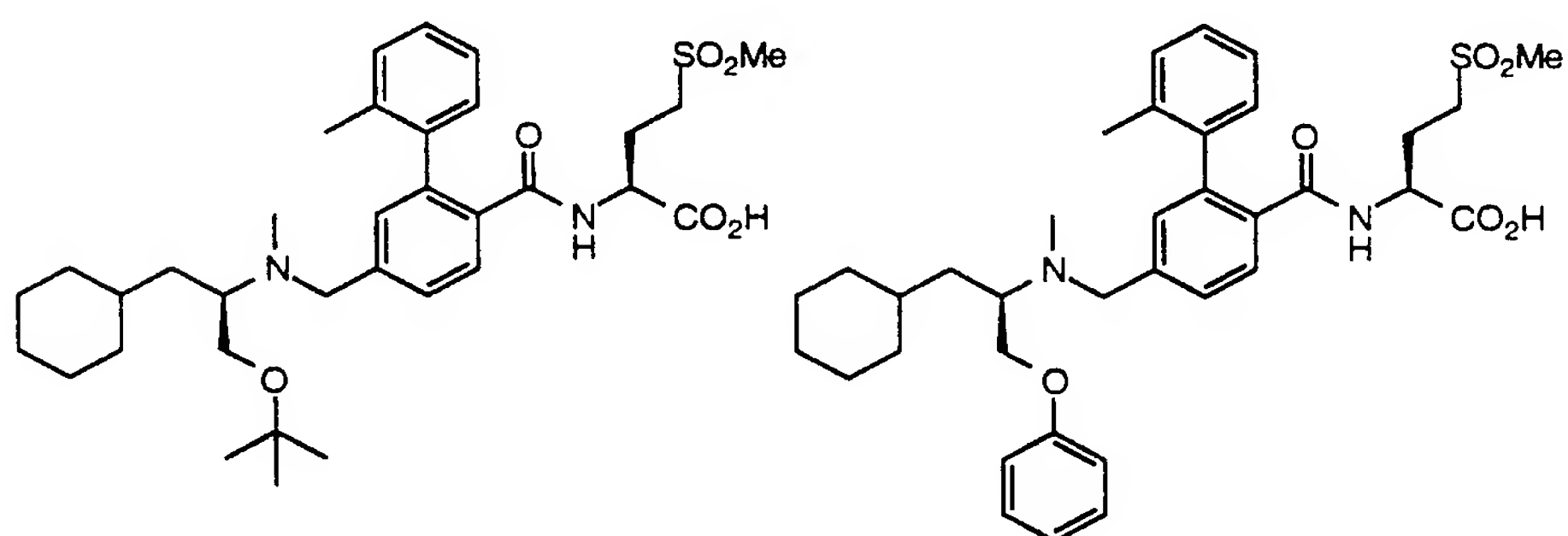
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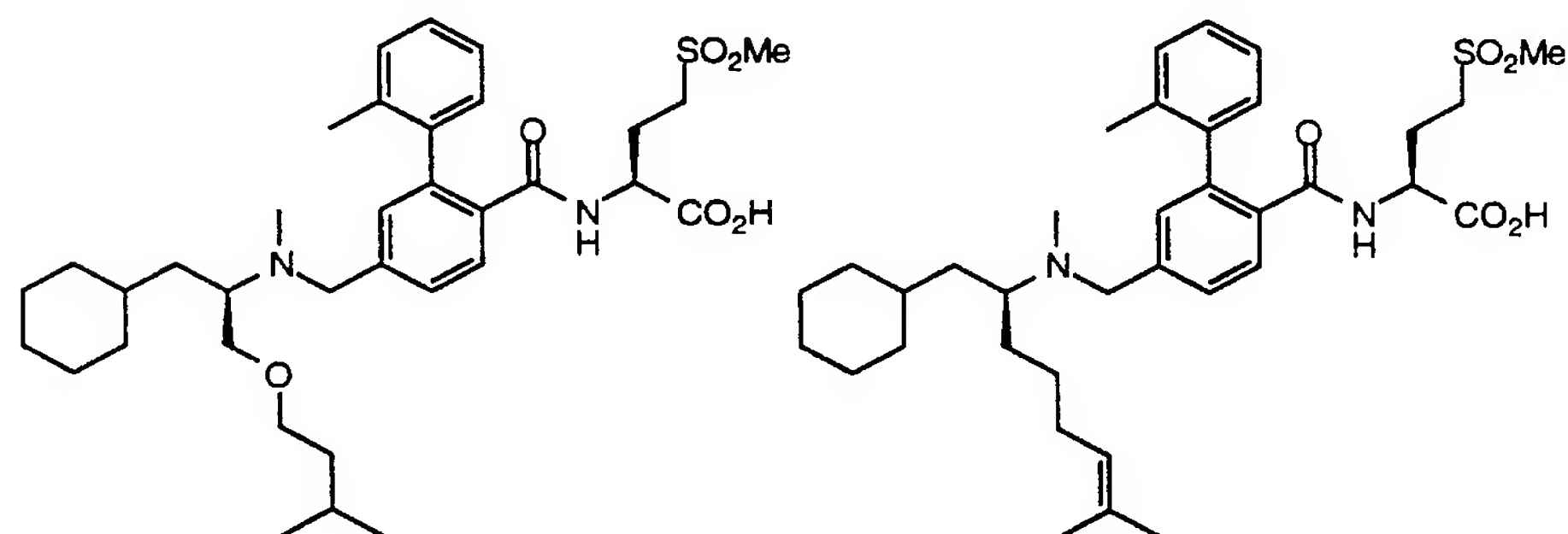
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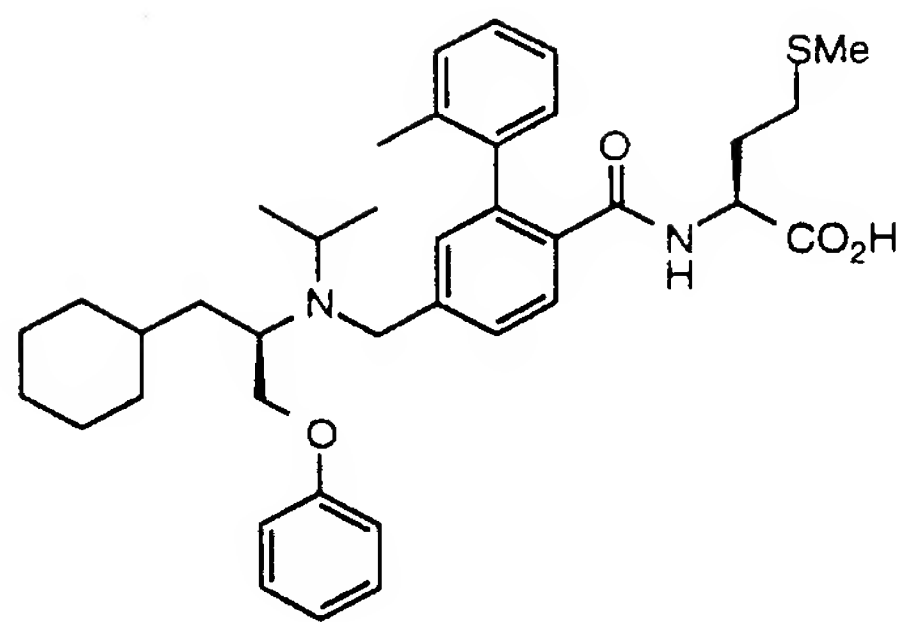
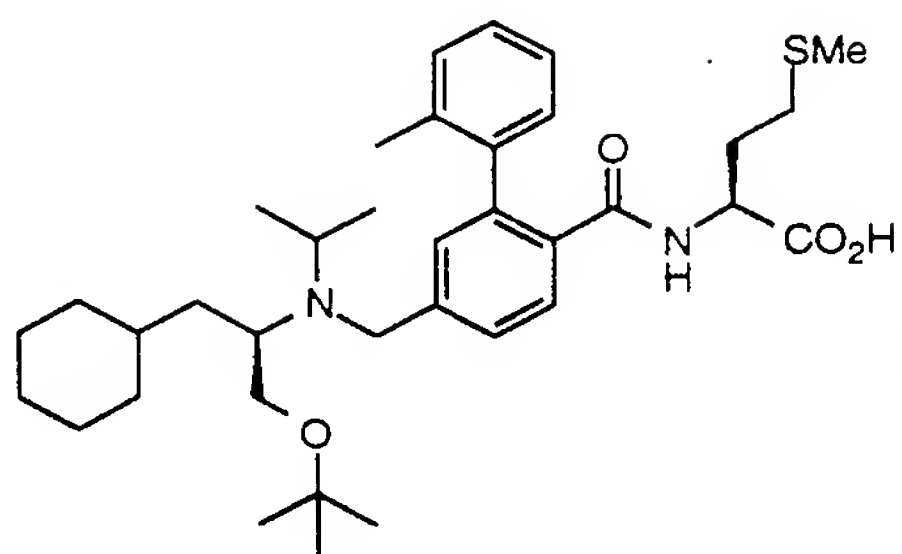
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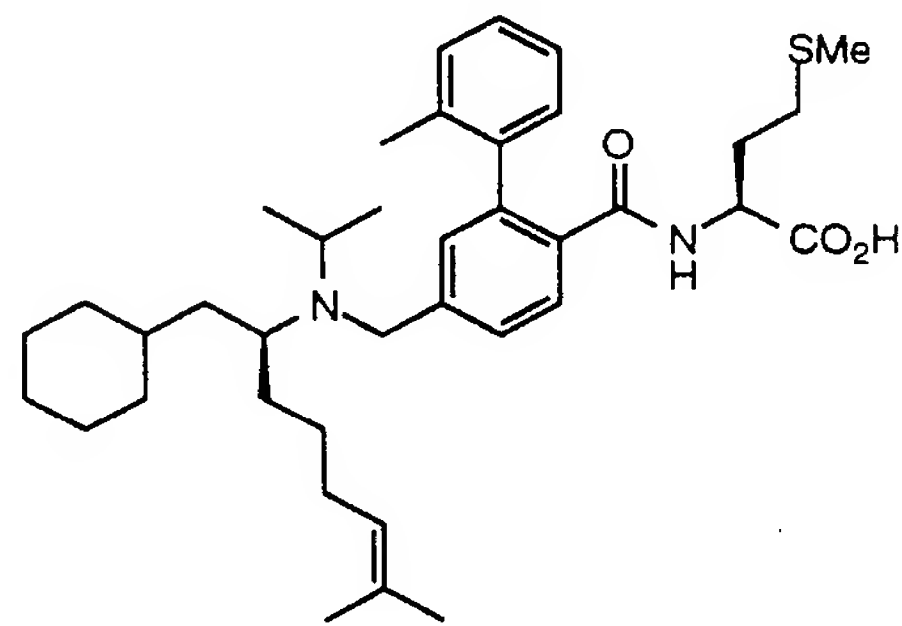
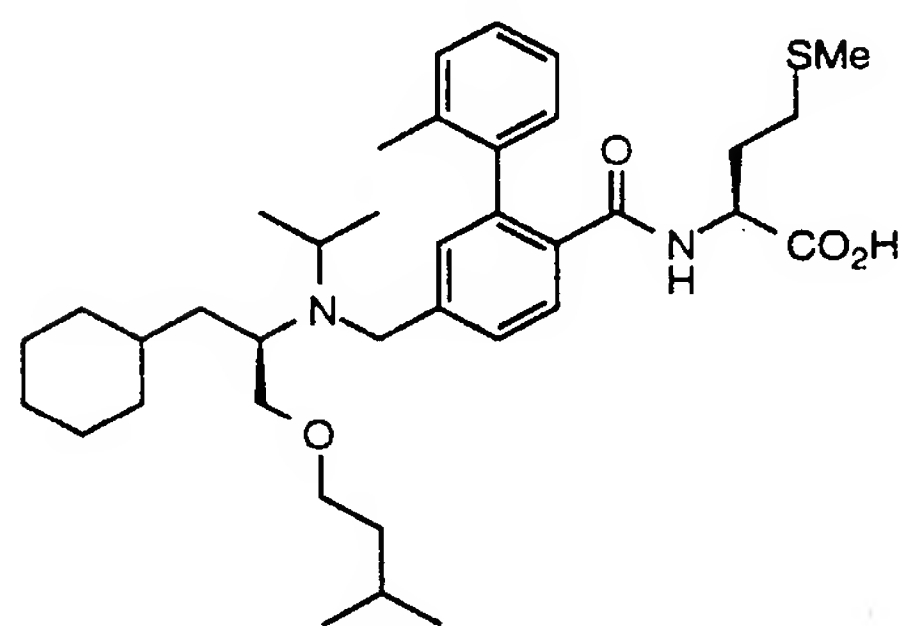
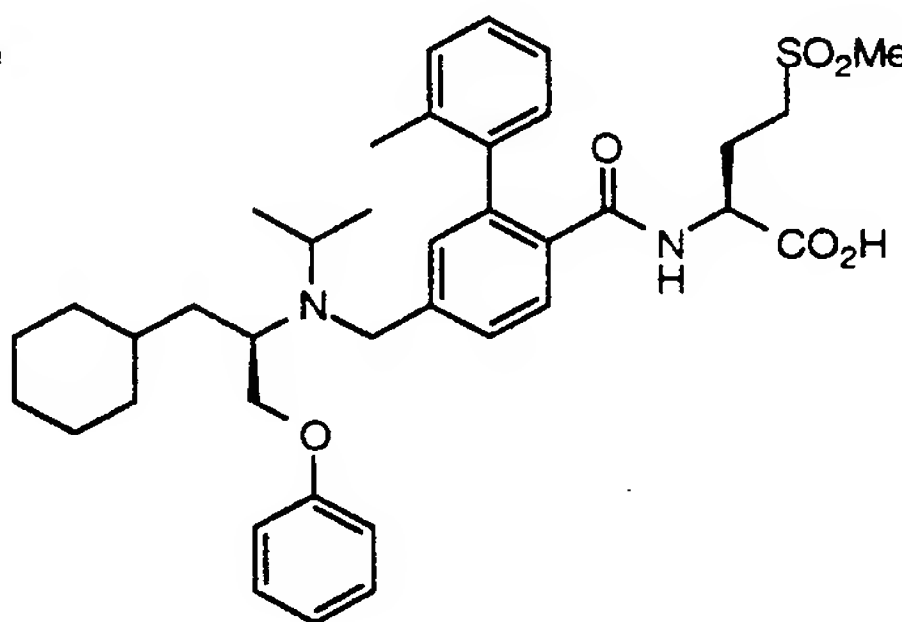
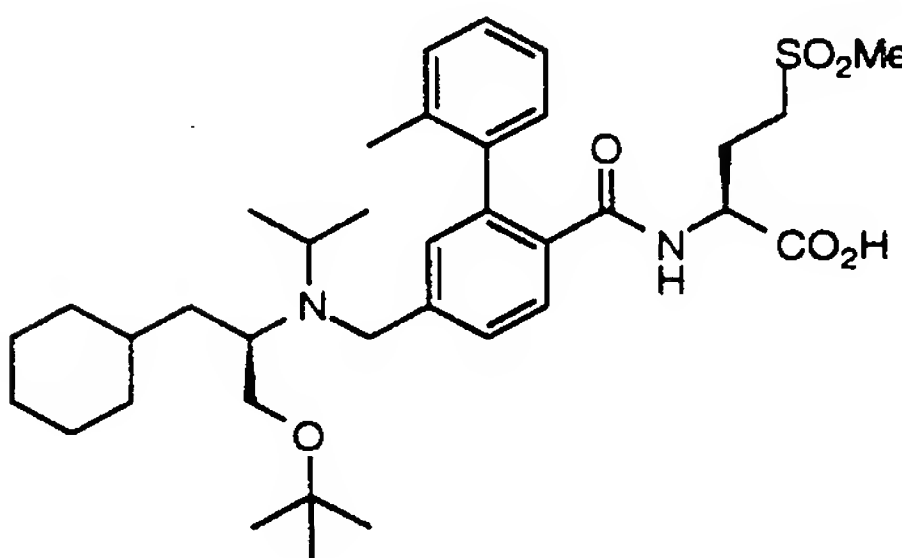
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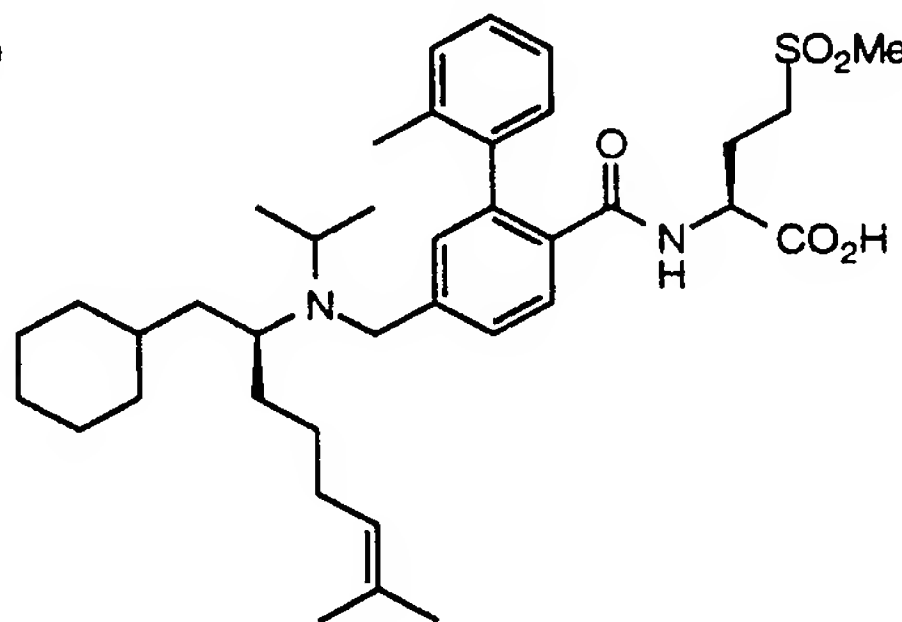
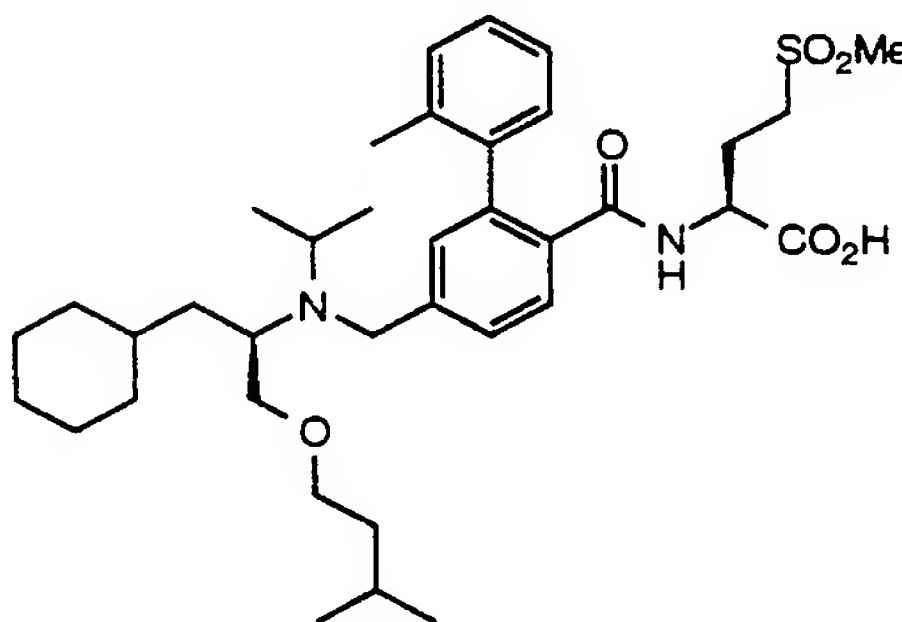
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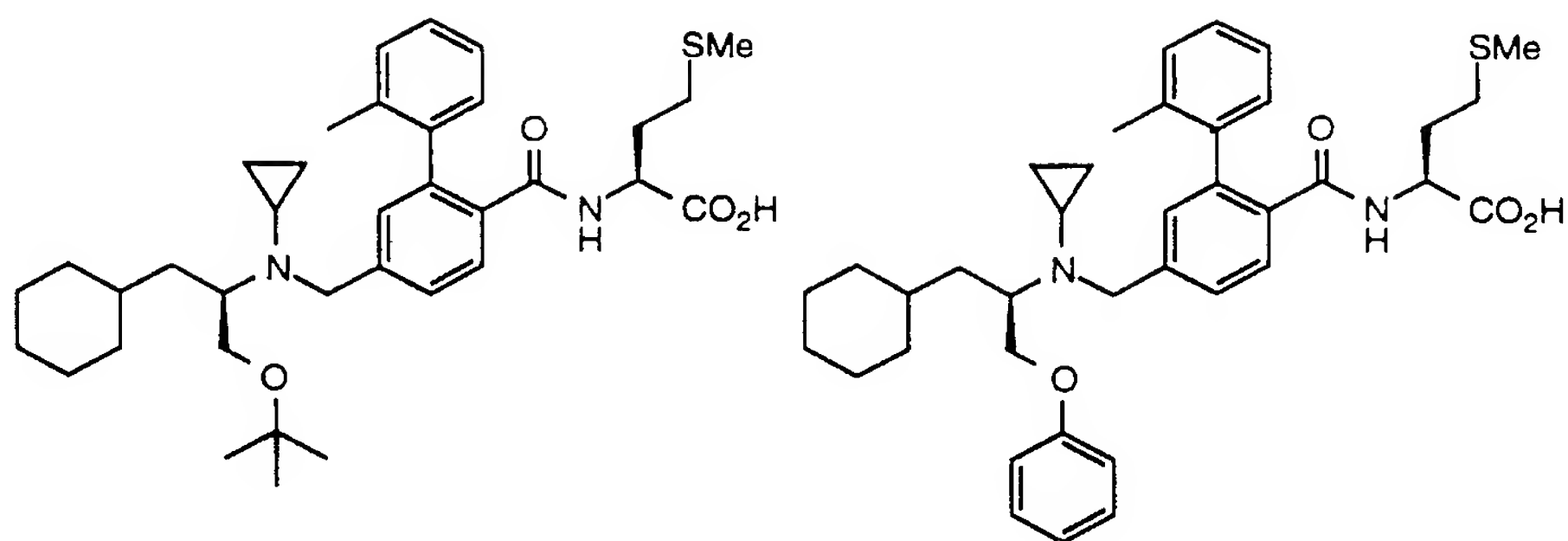
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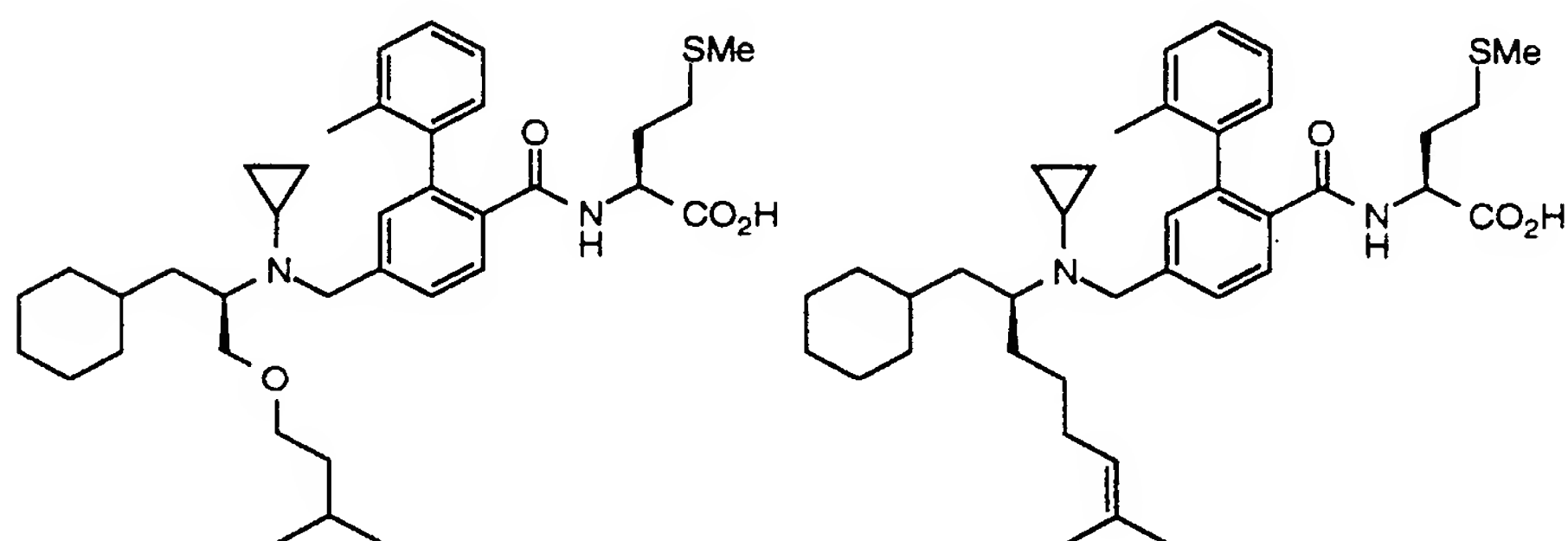
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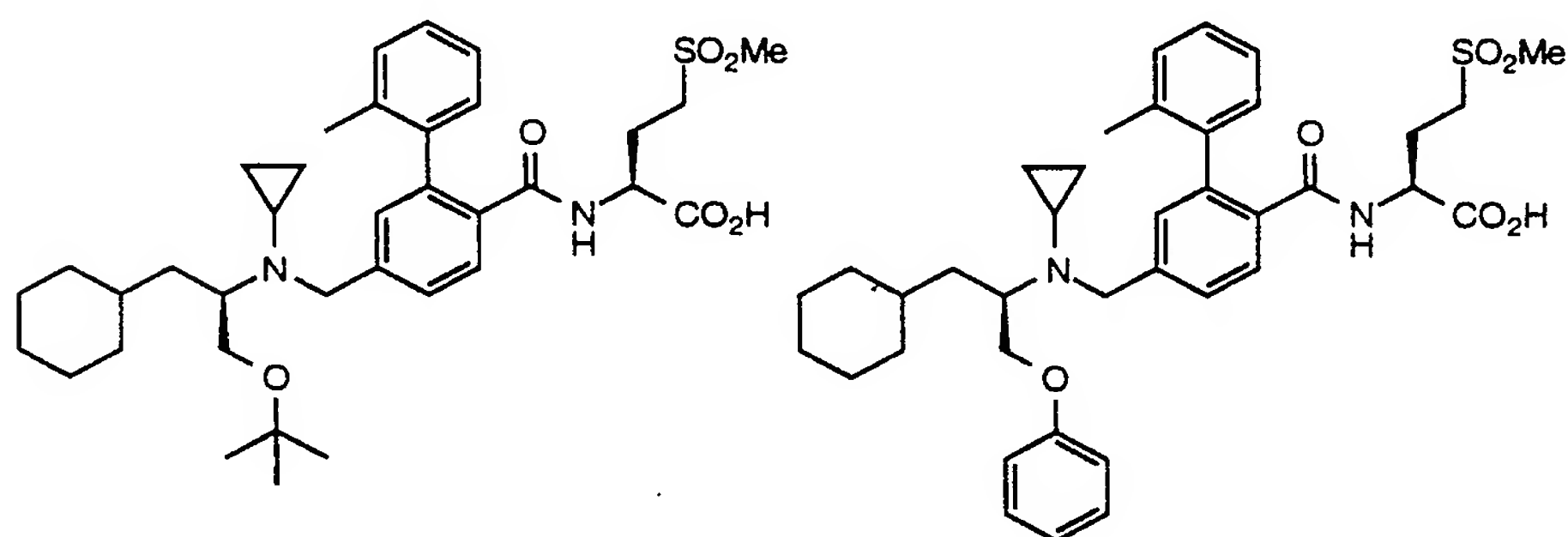
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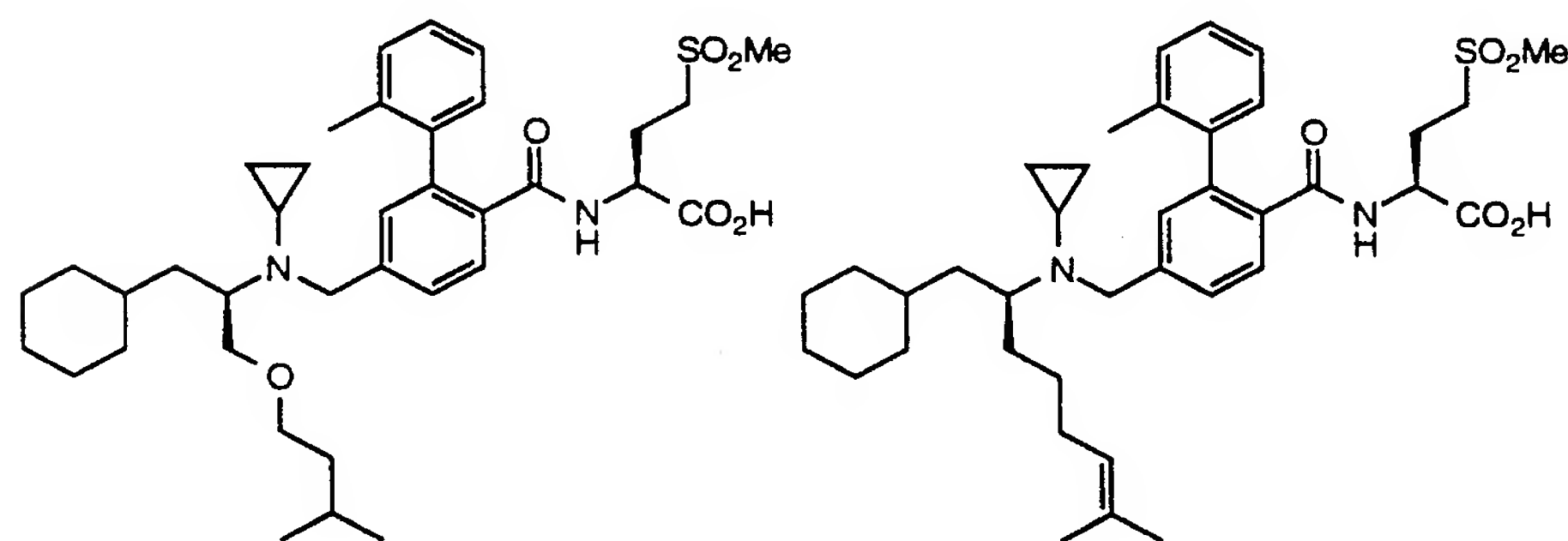
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375 376



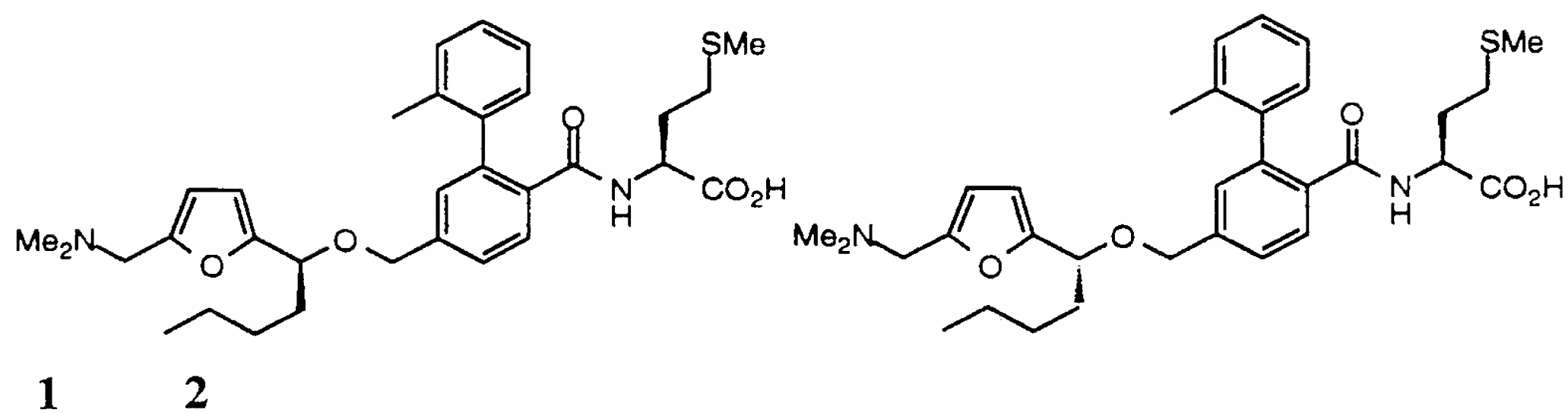
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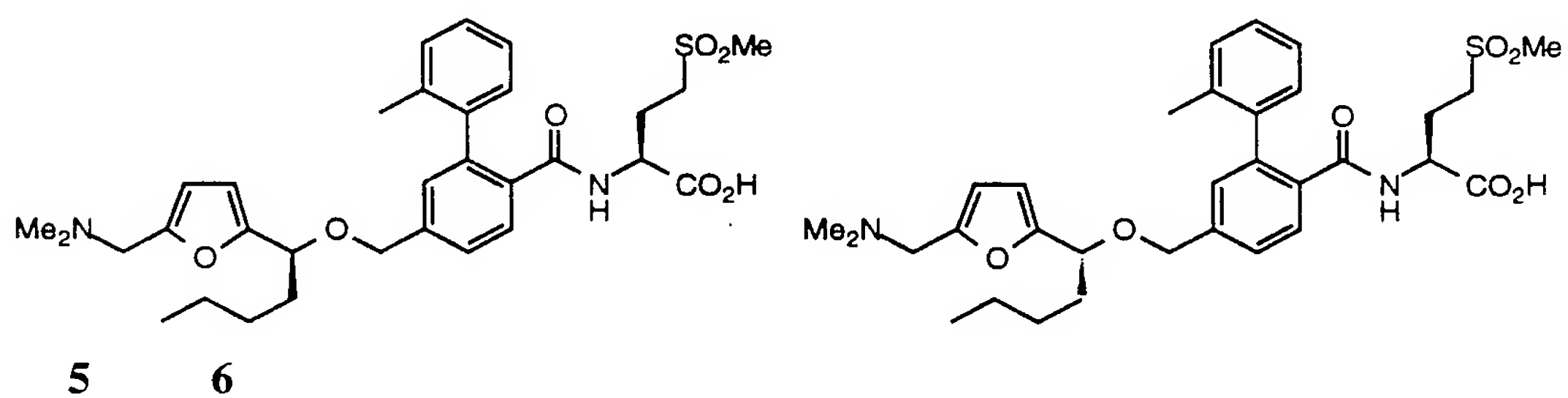
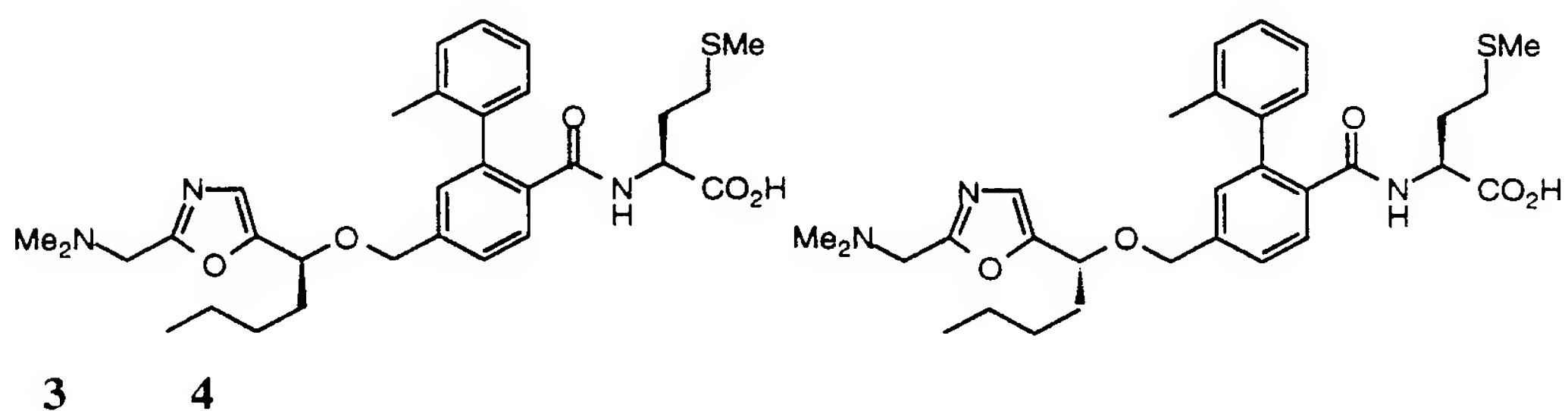
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Table 7. Ethers of the Type A-OL<sub>1</sub>

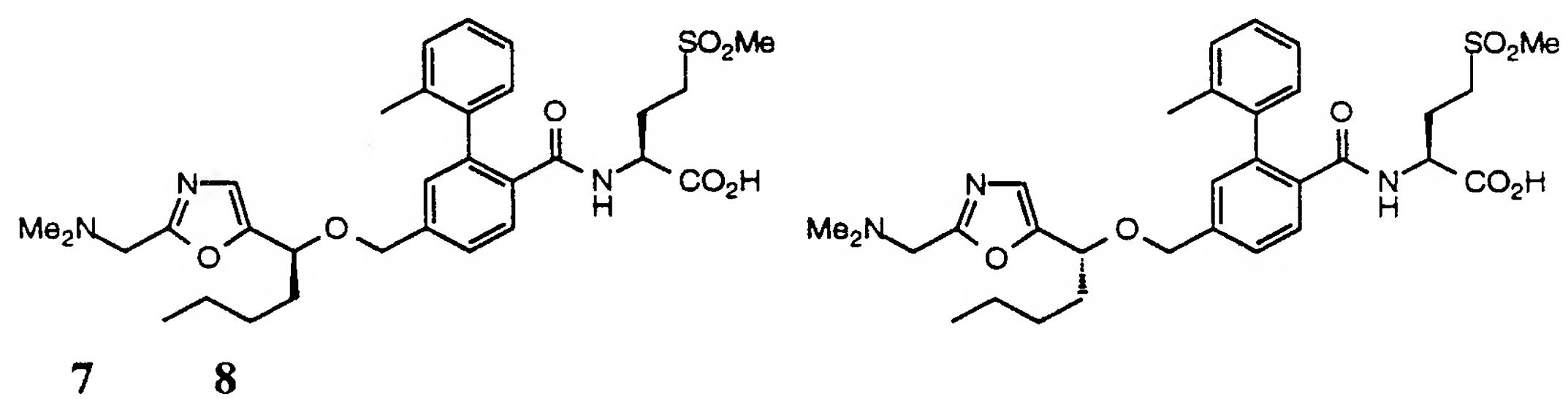
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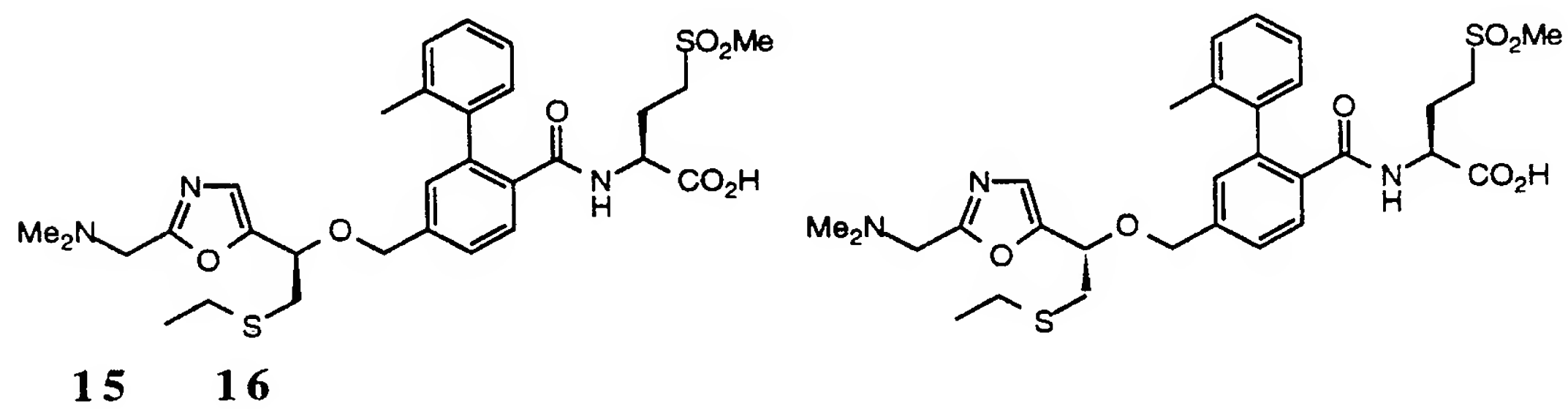
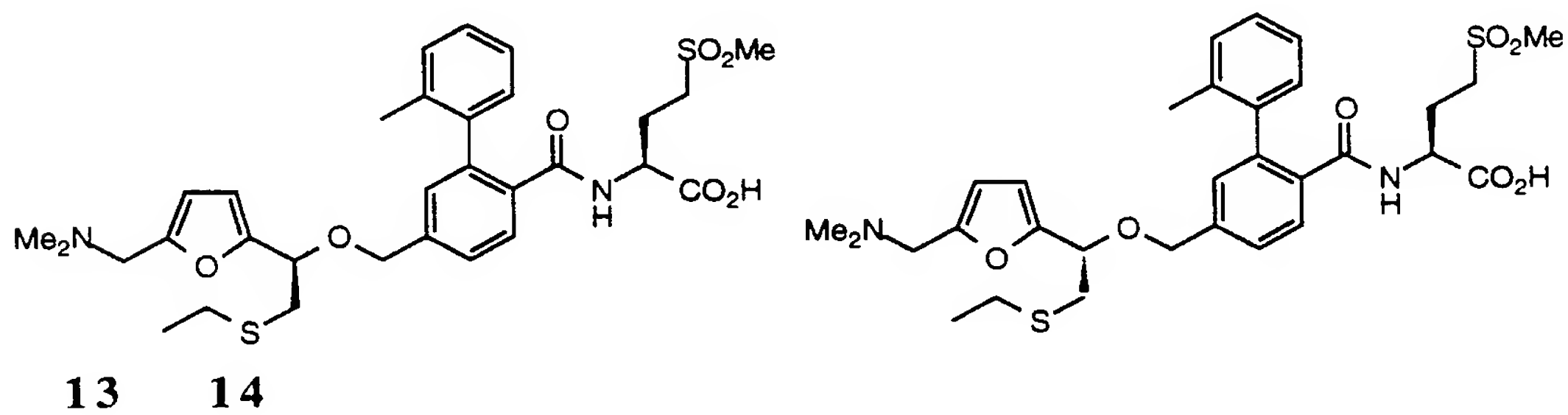
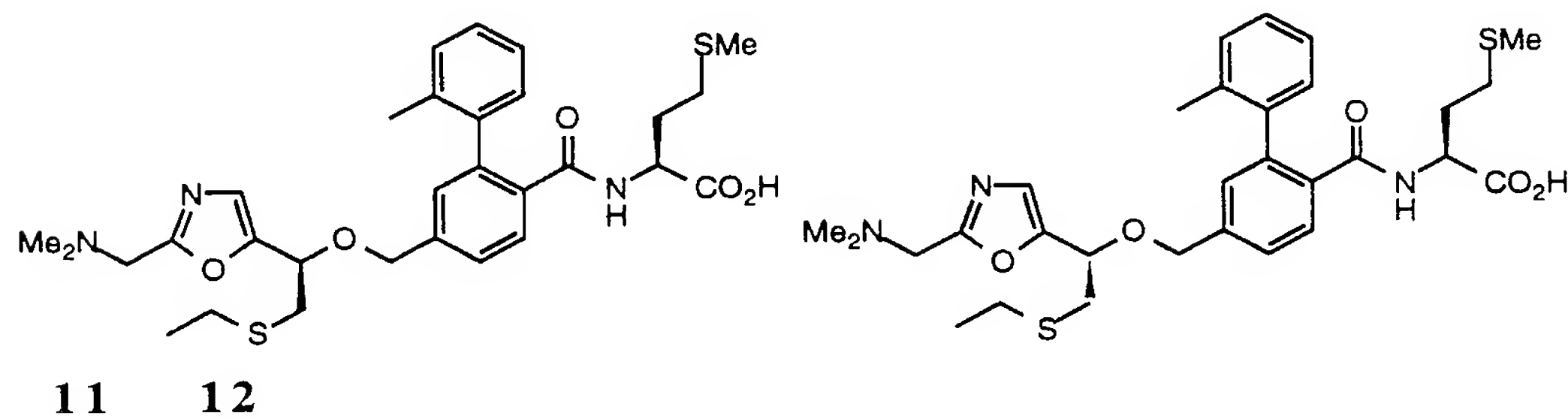
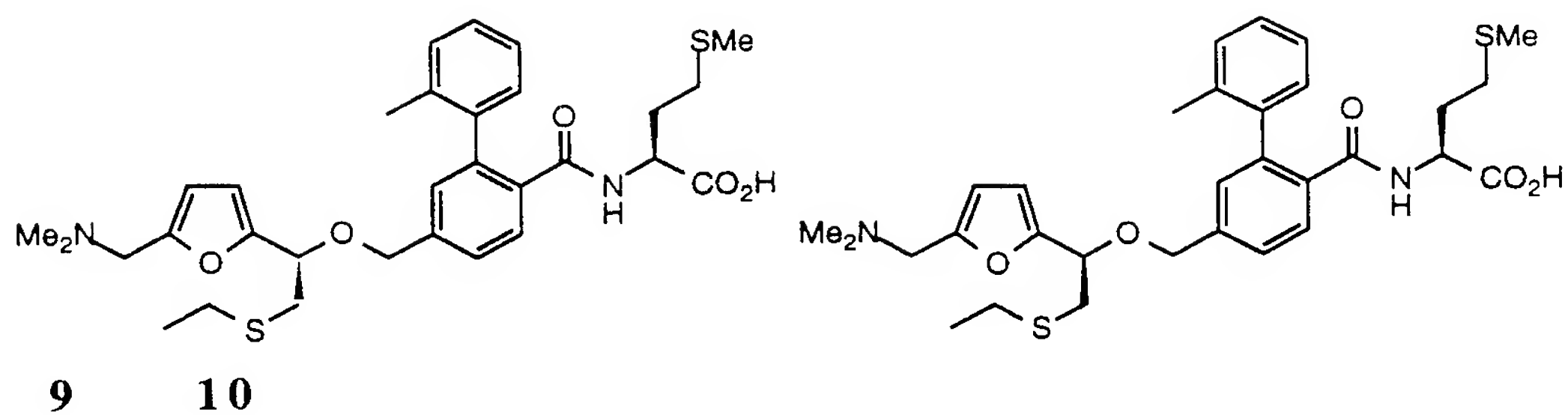
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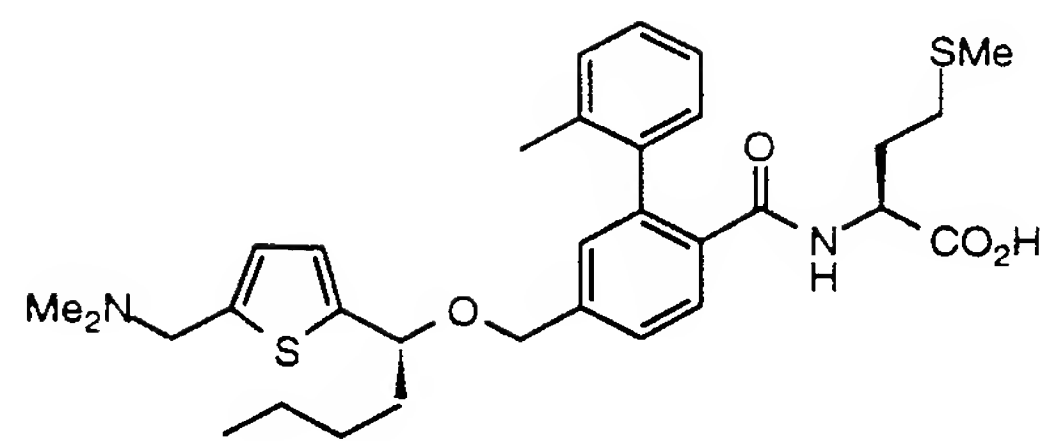
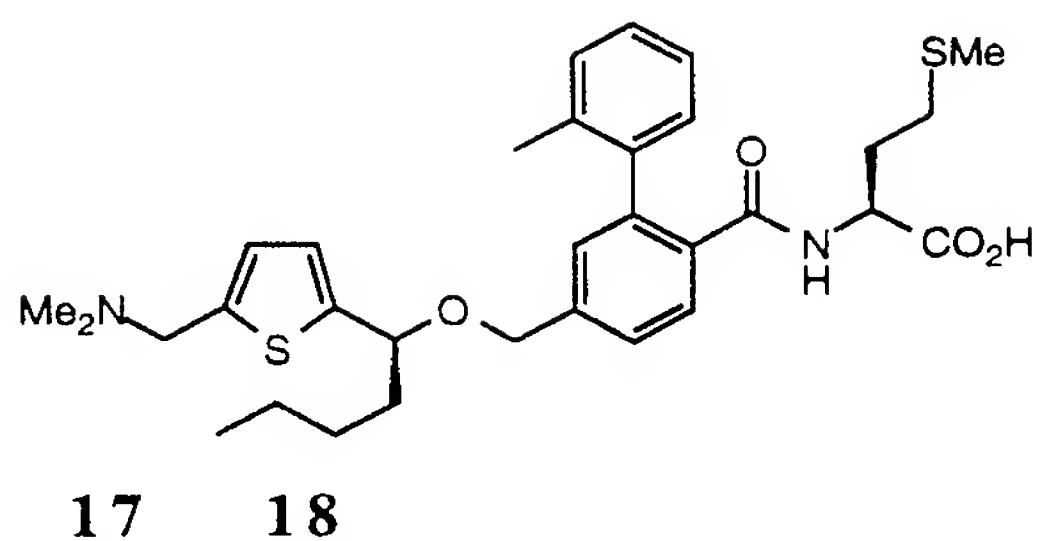
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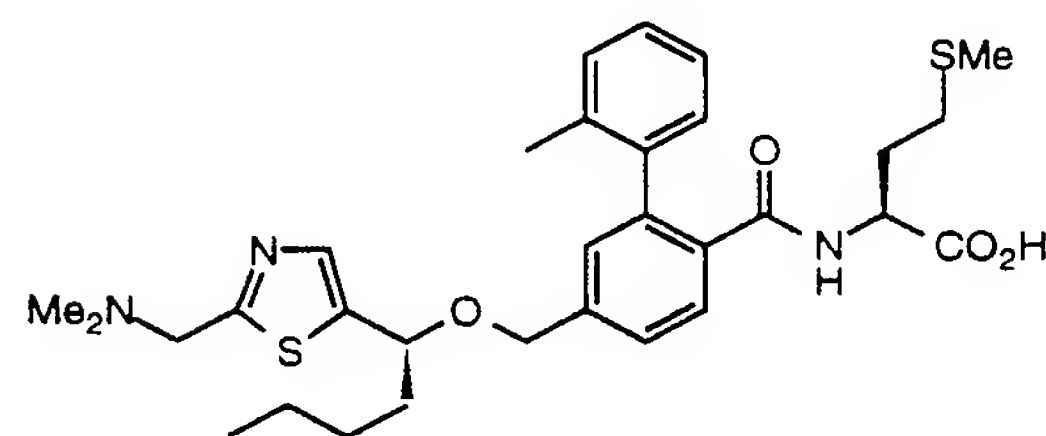
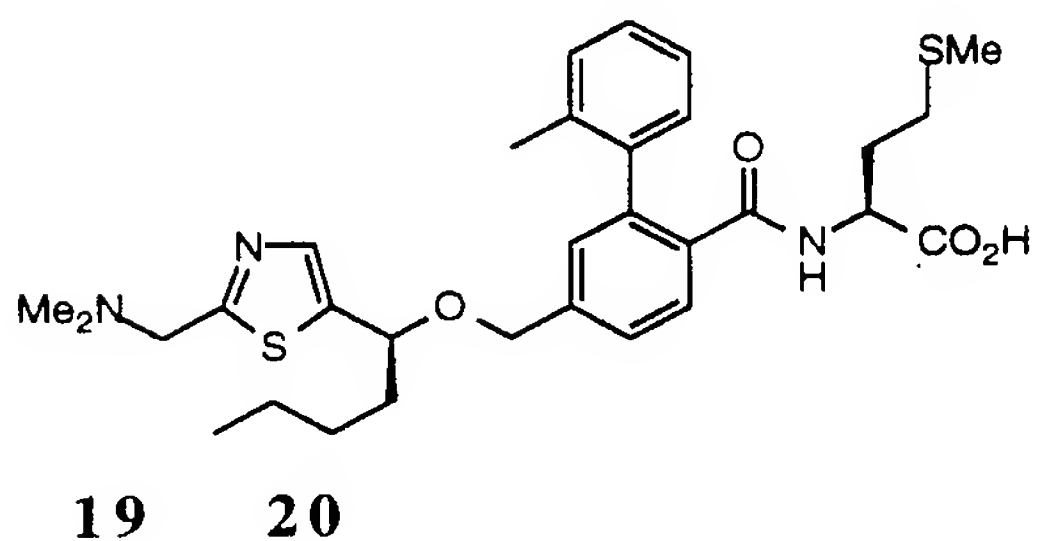




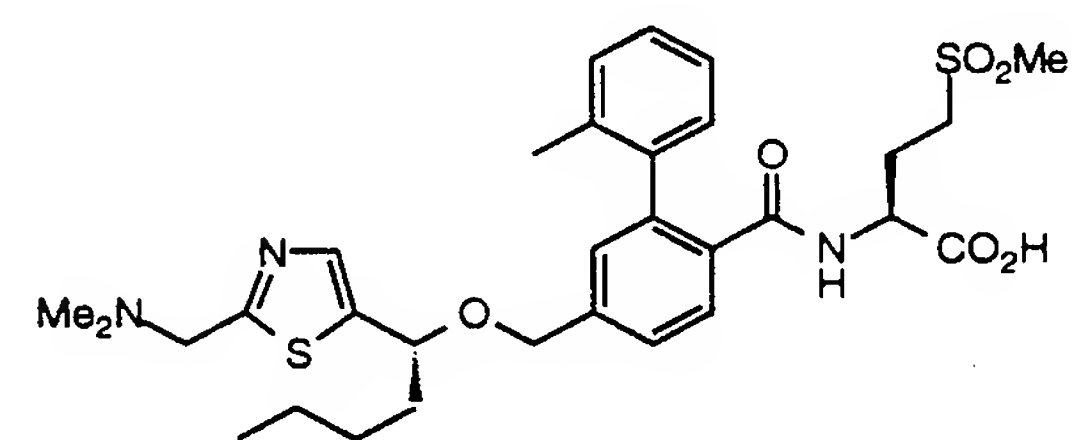
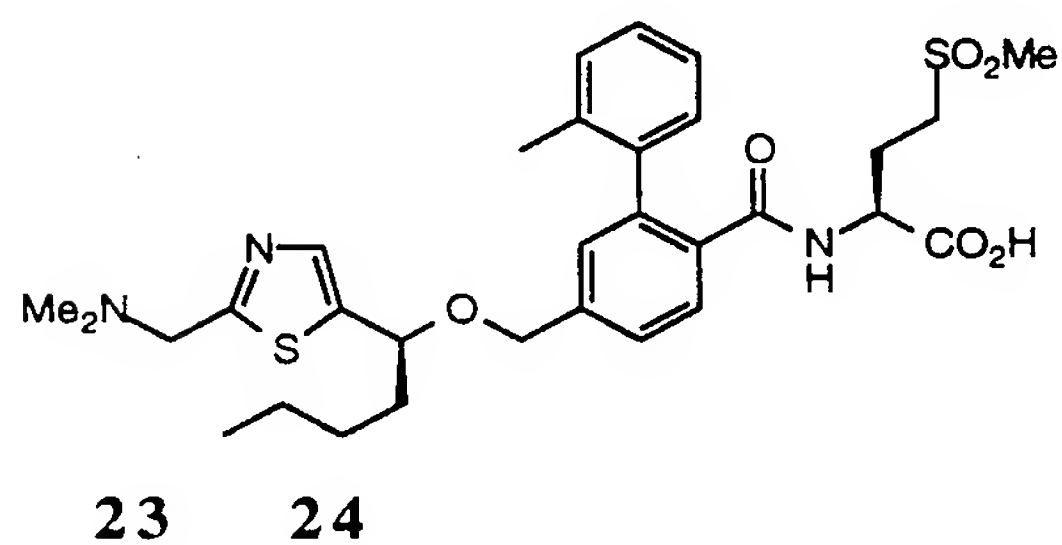
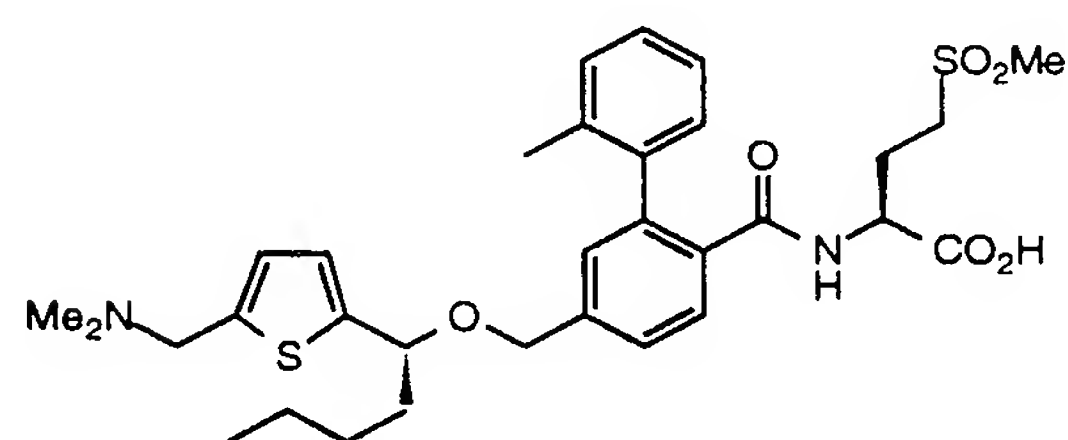
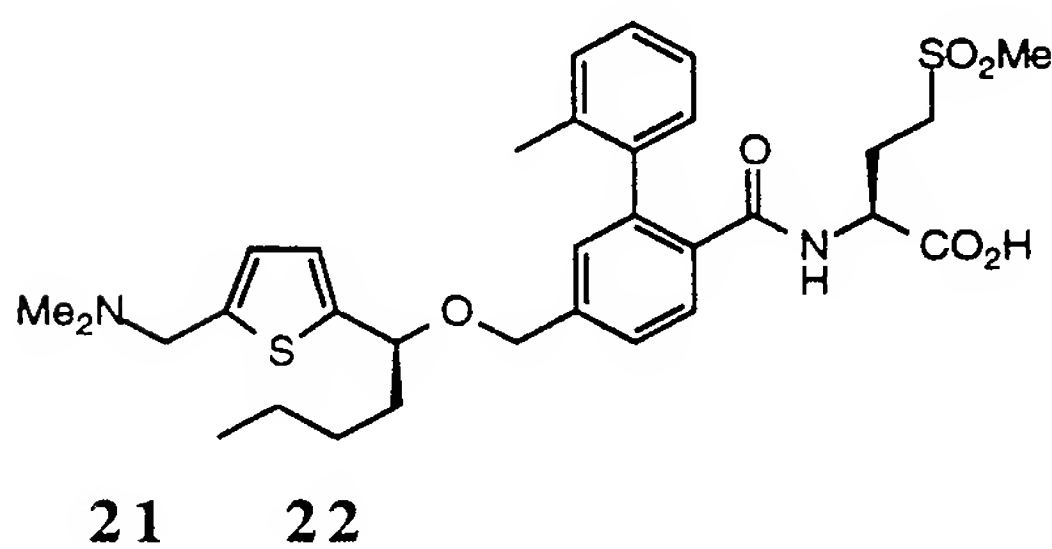
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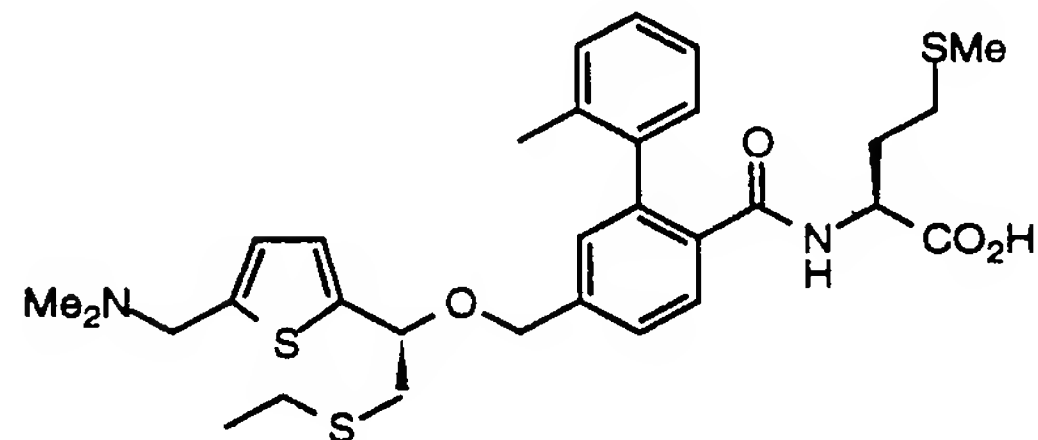
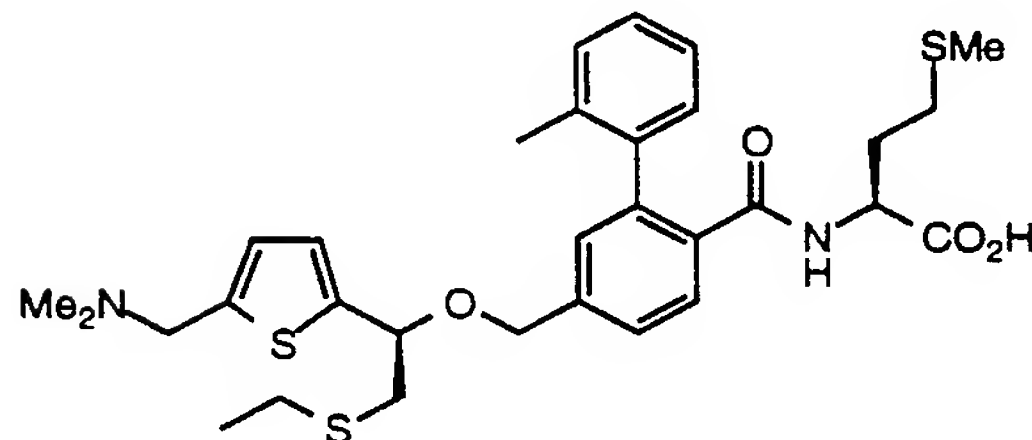
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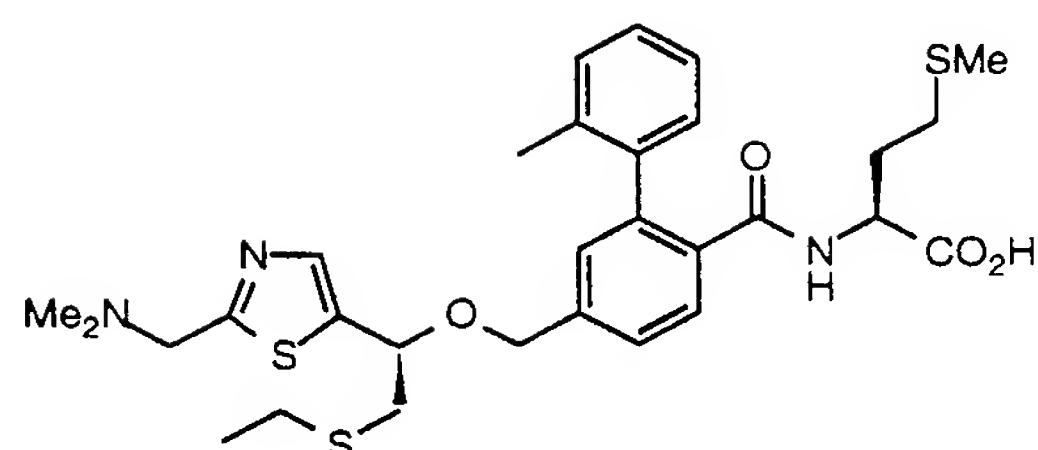
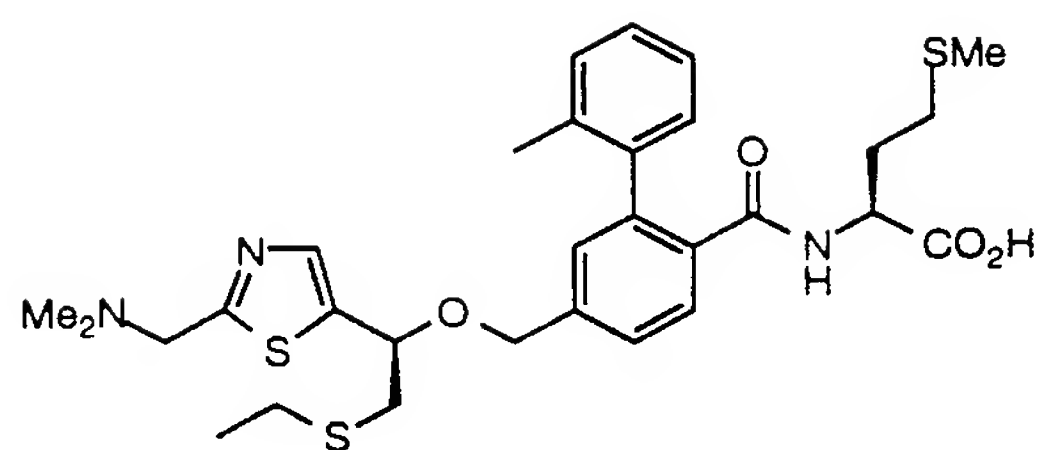
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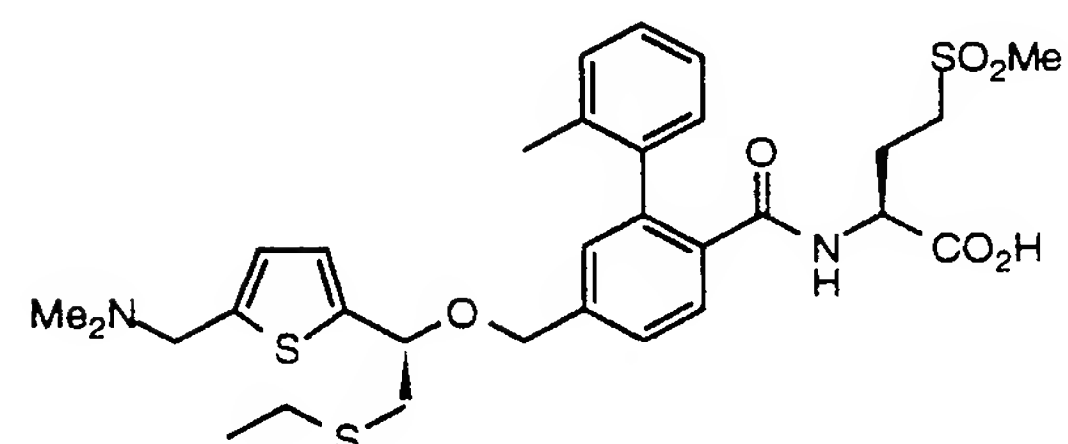
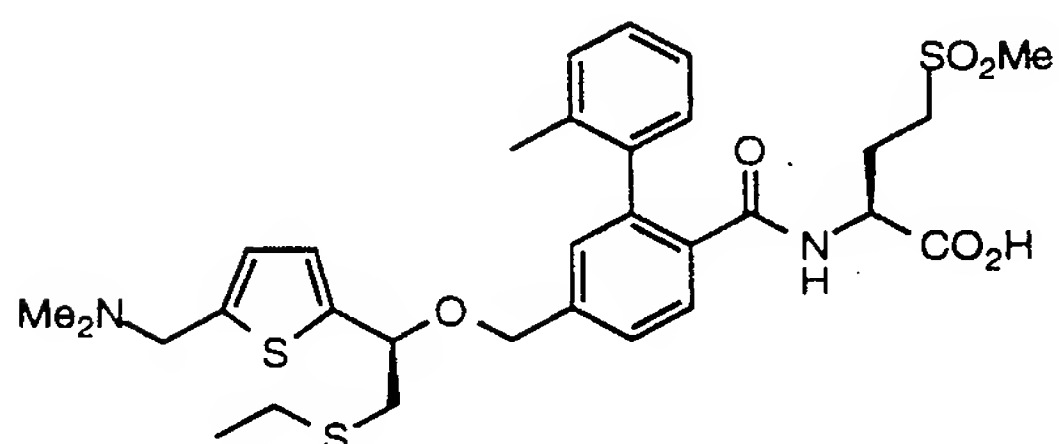


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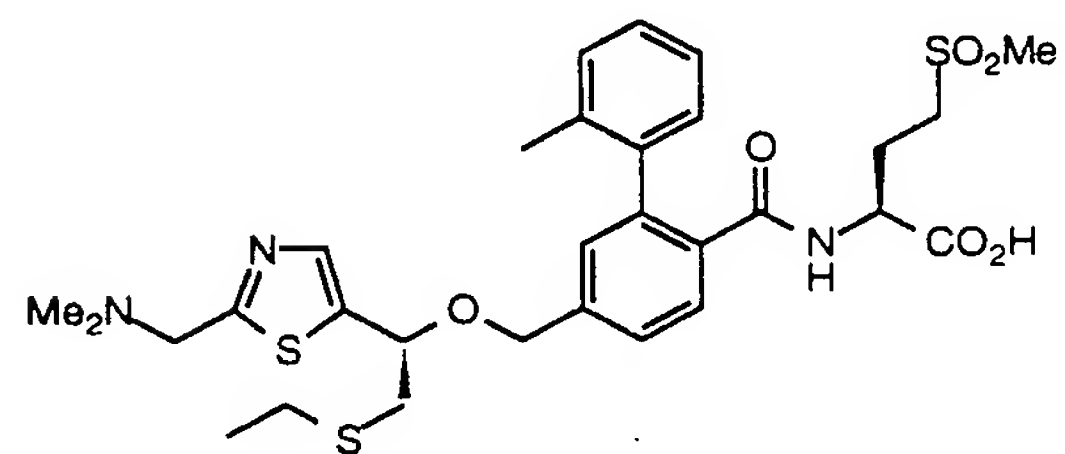
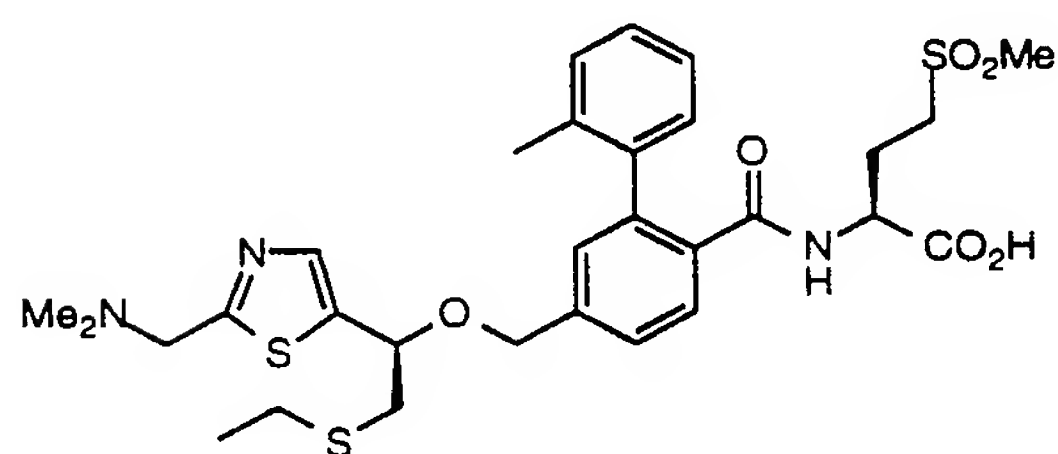
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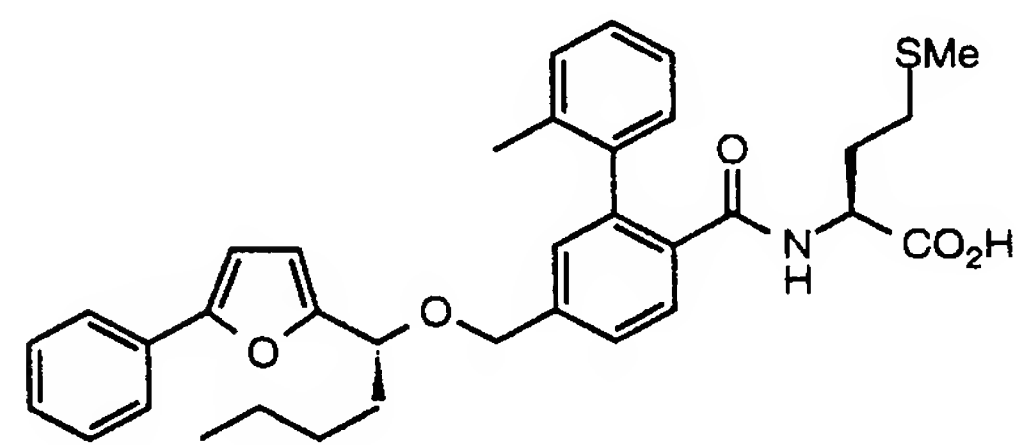
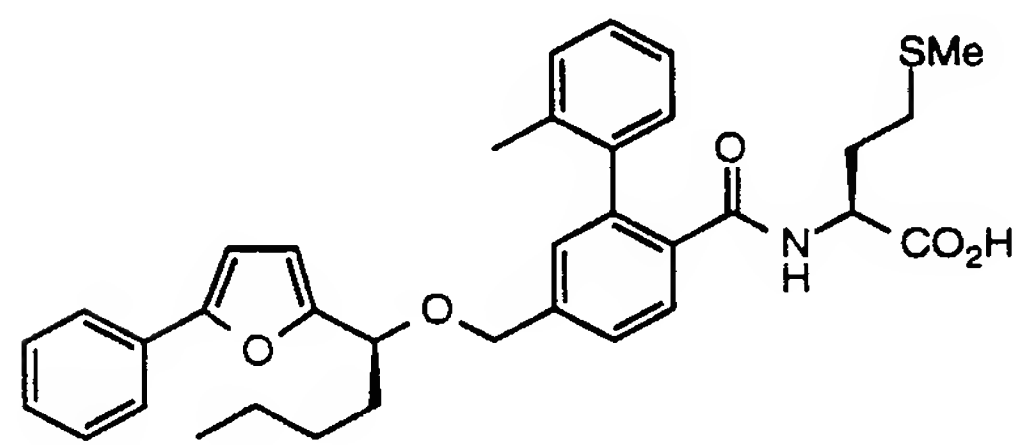
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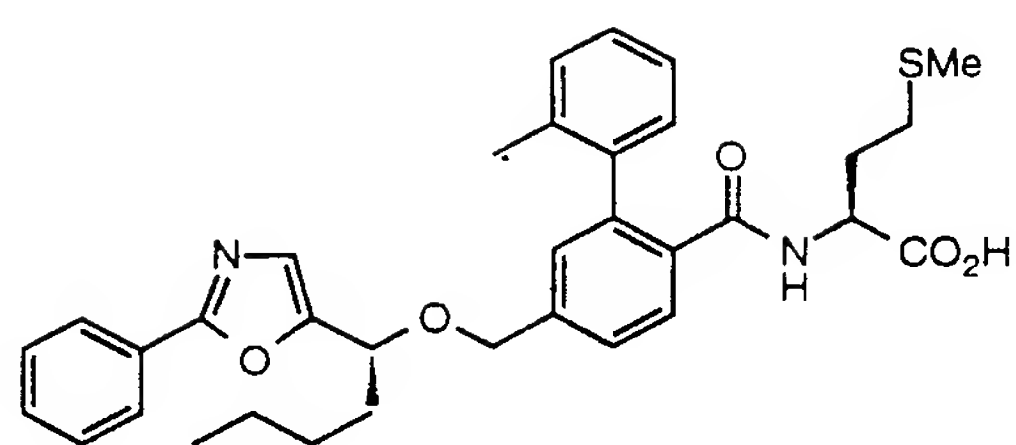
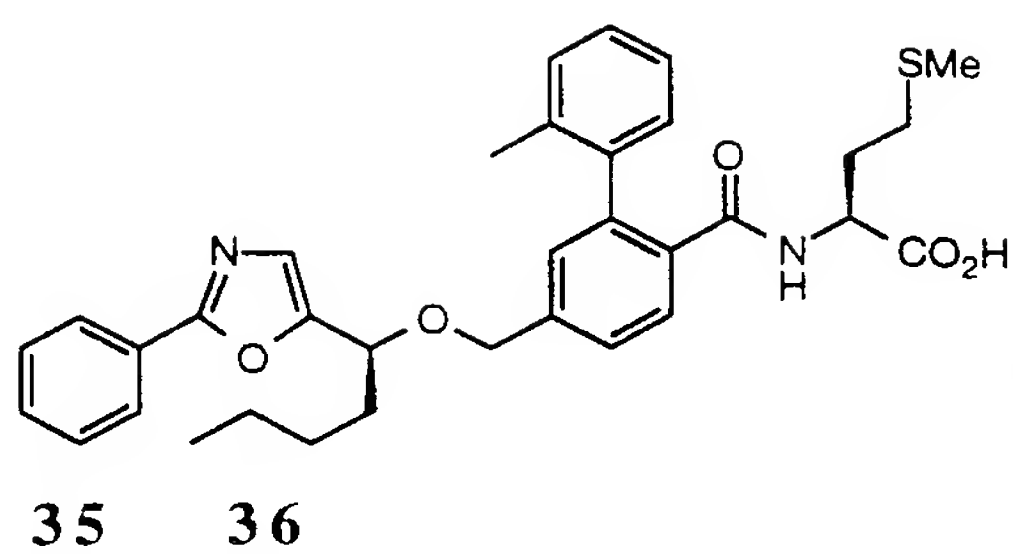
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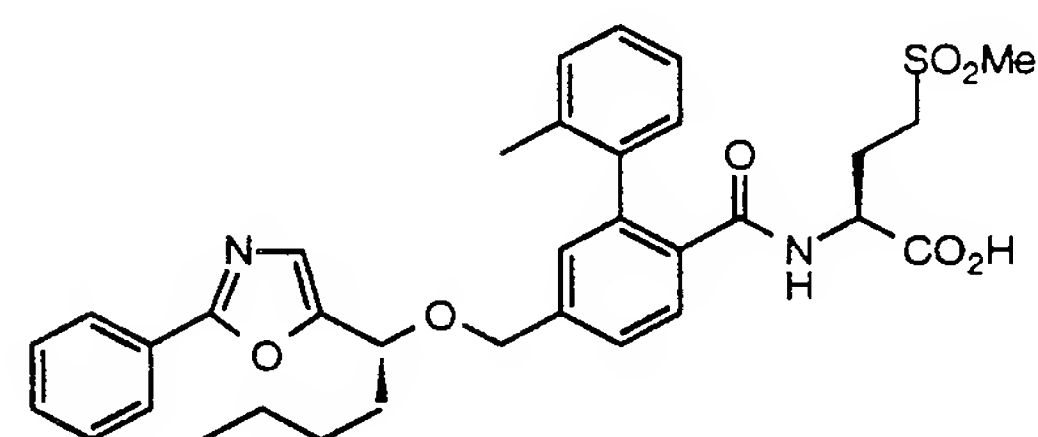
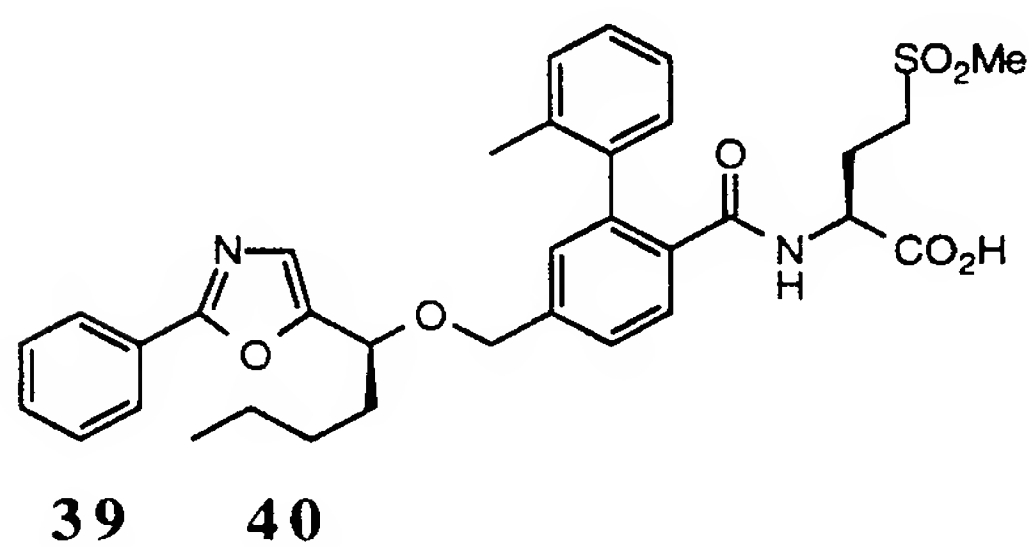
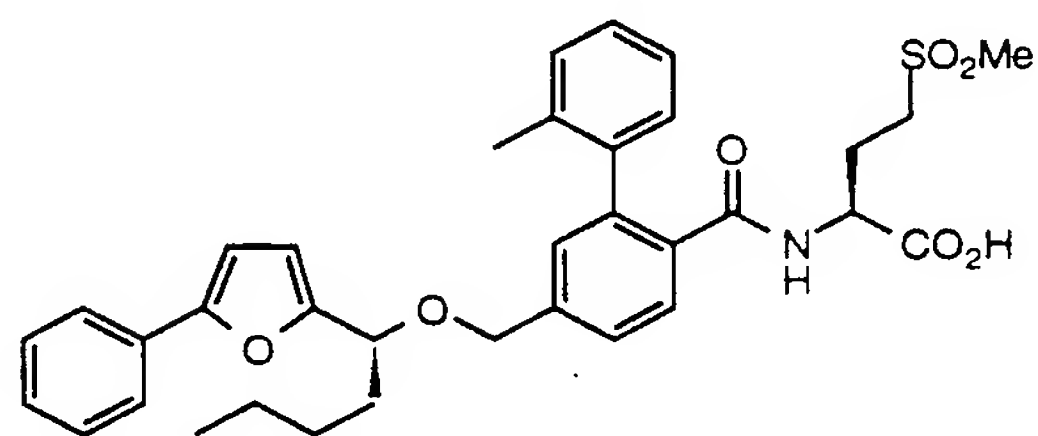
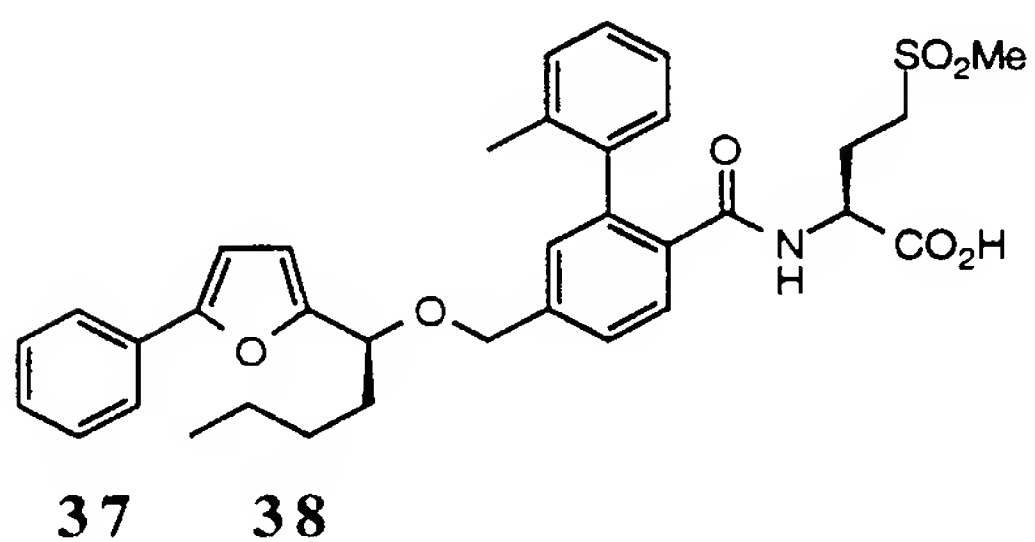


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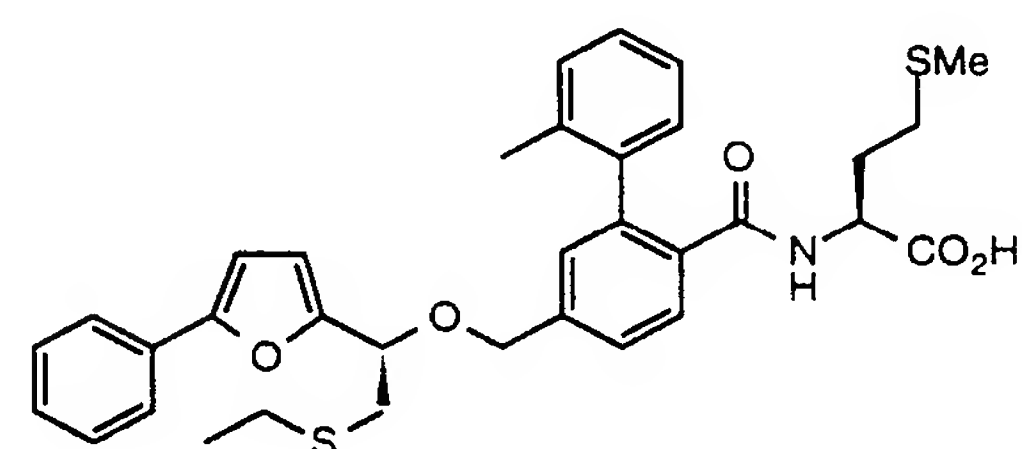
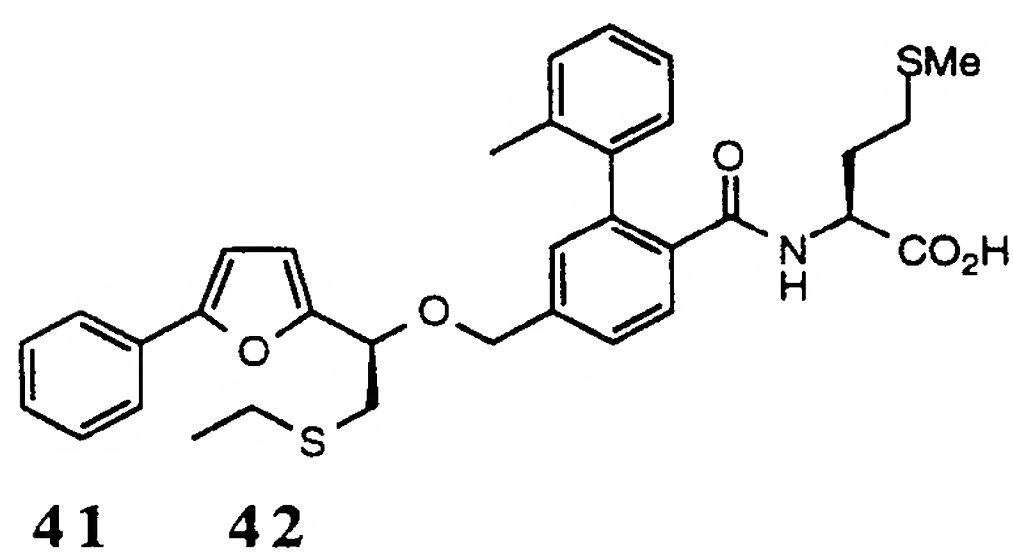
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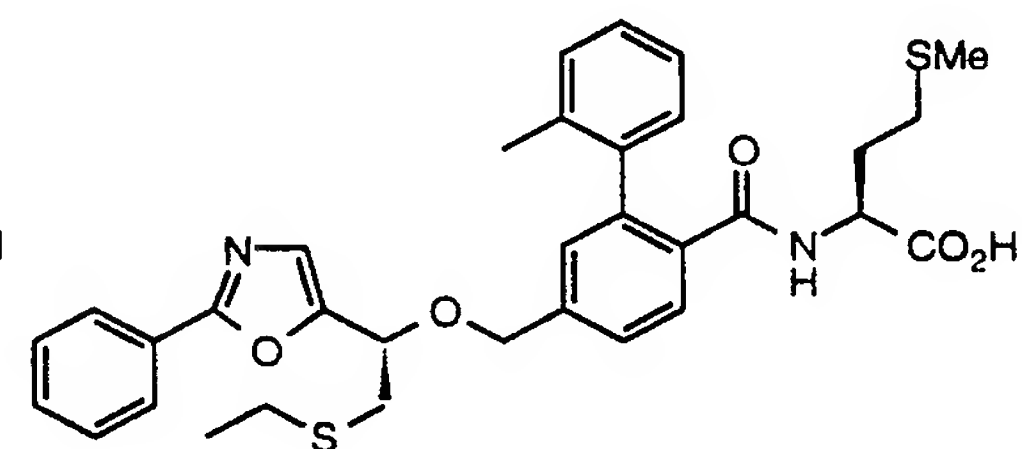
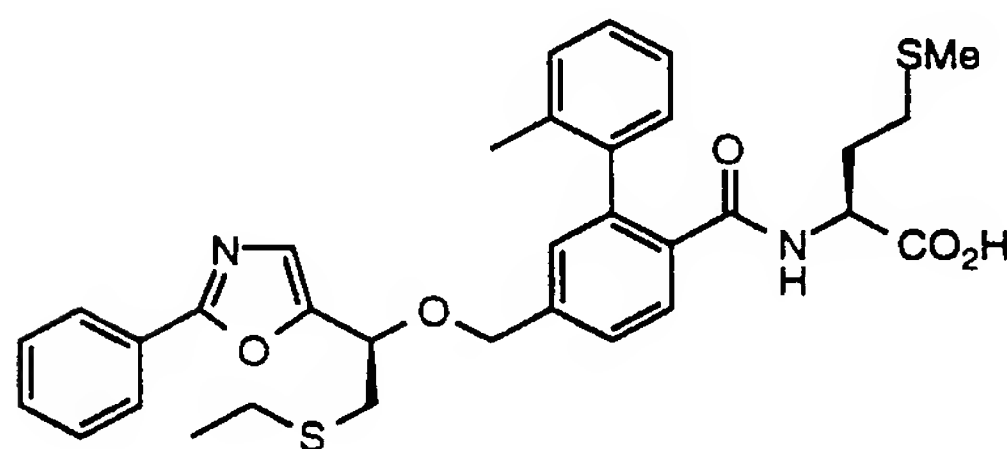
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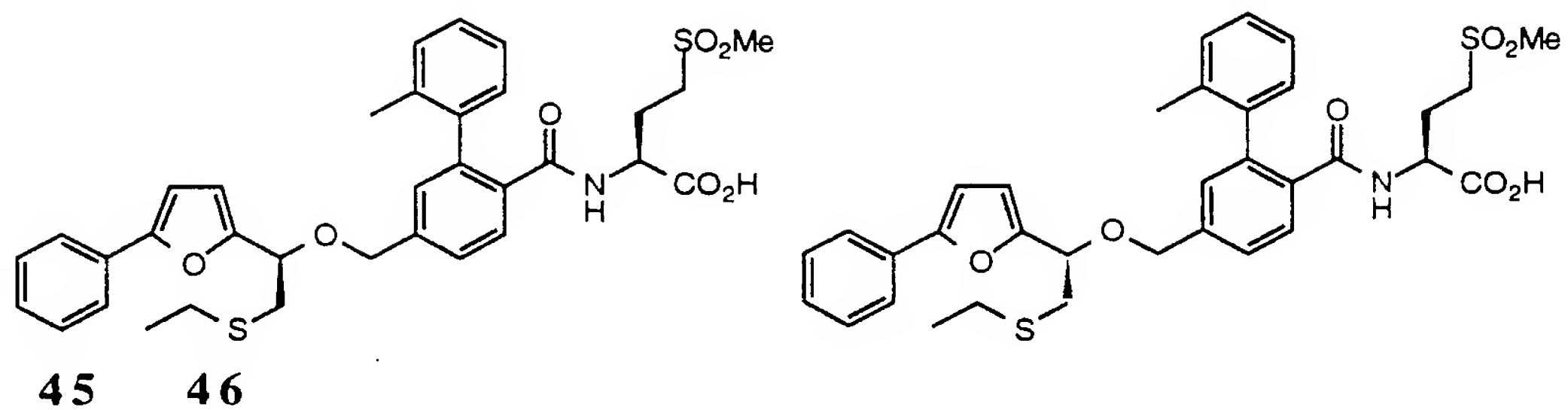


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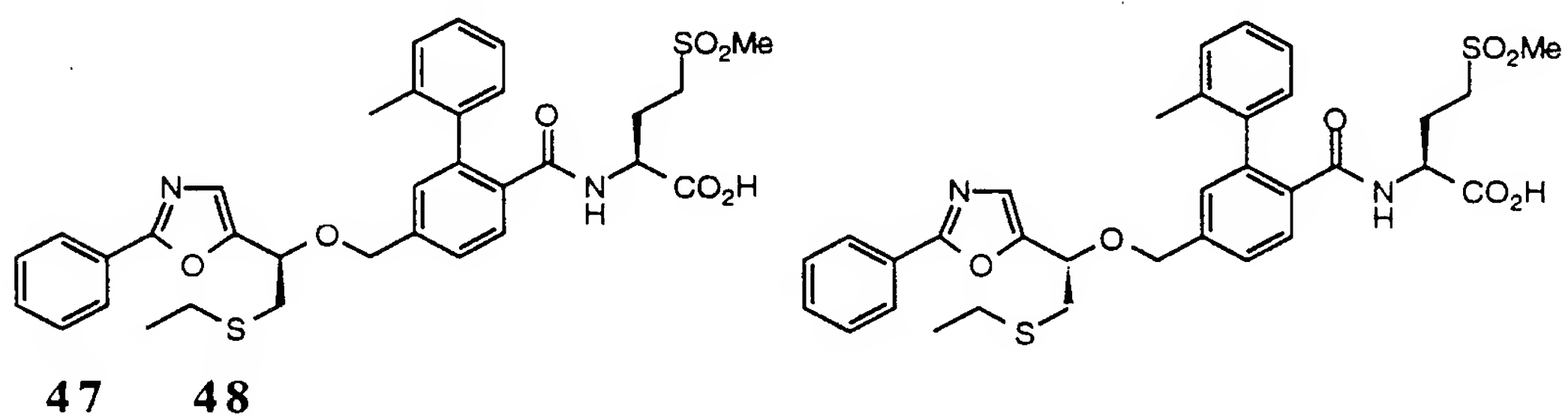


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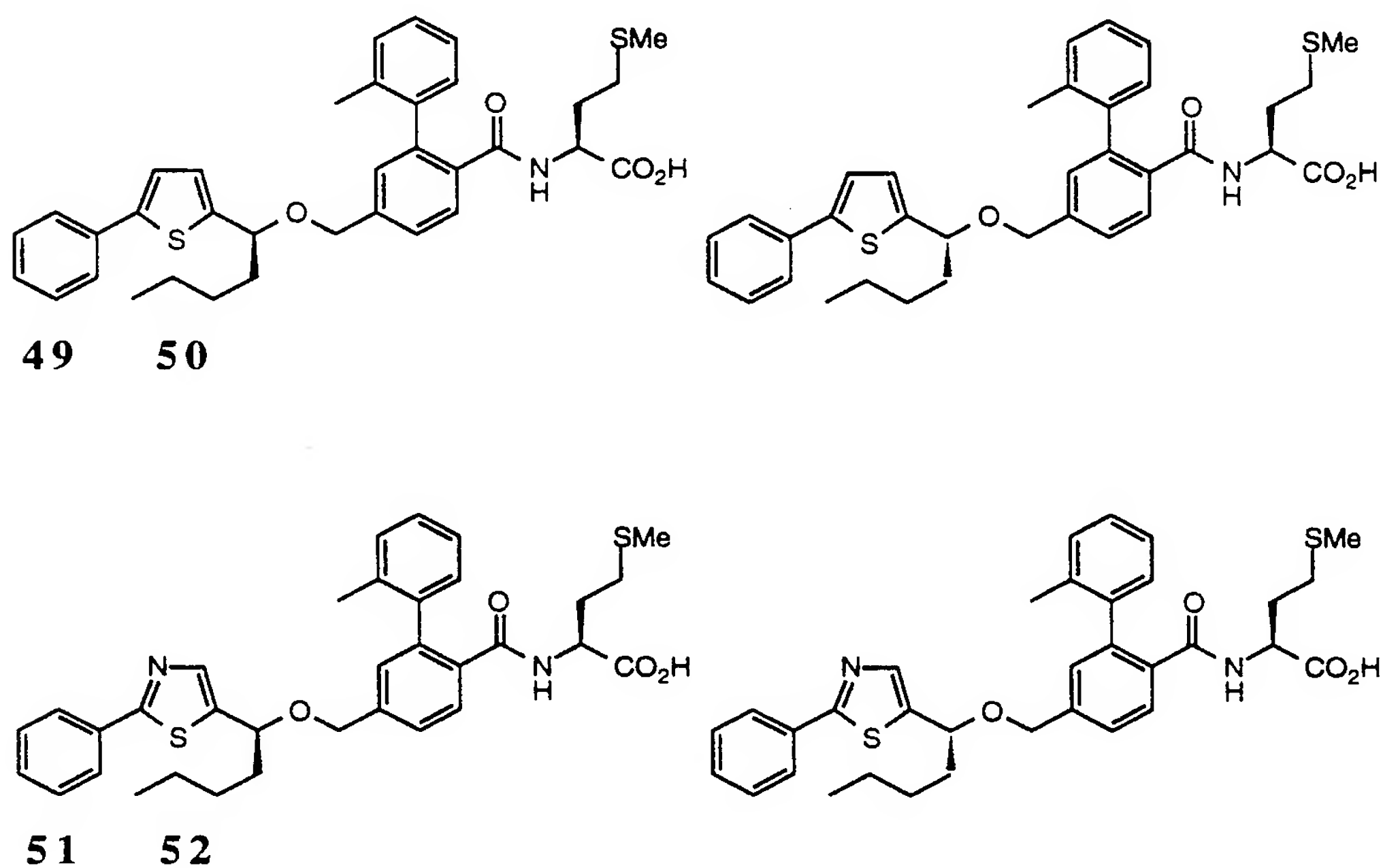
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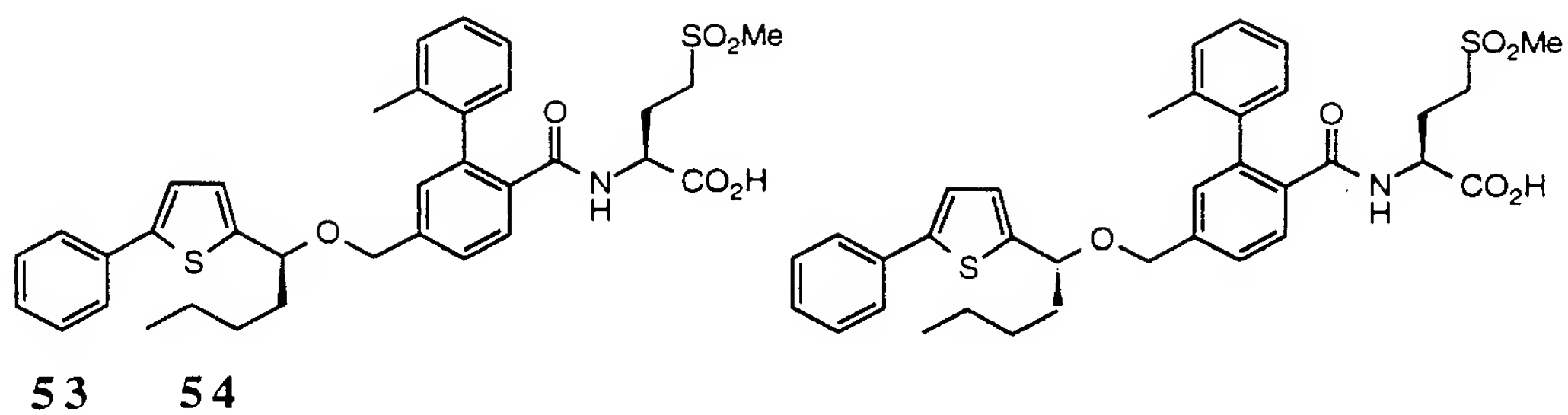
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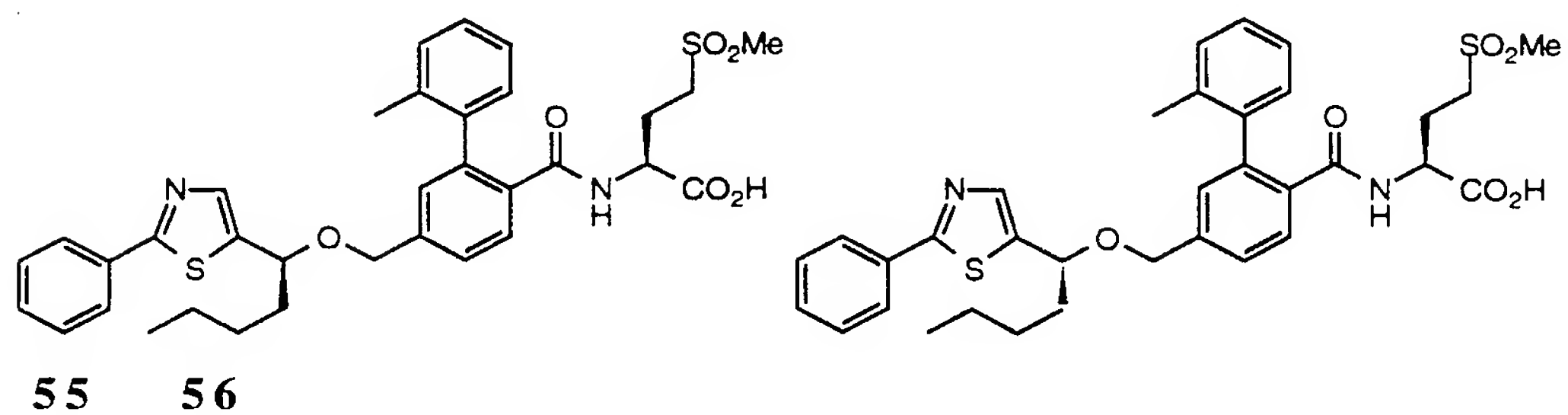
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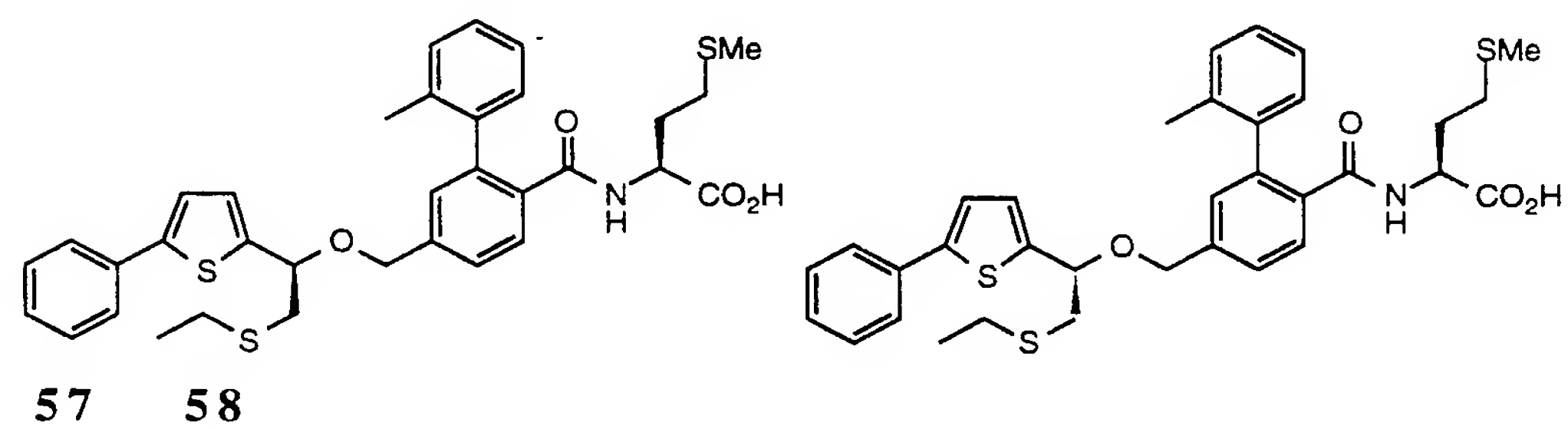
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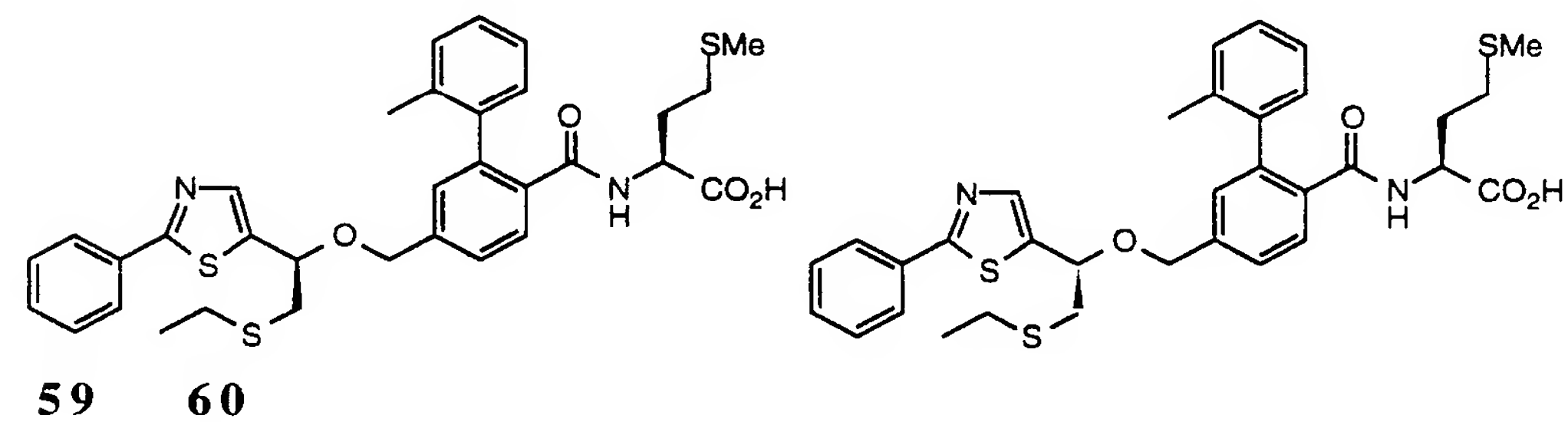
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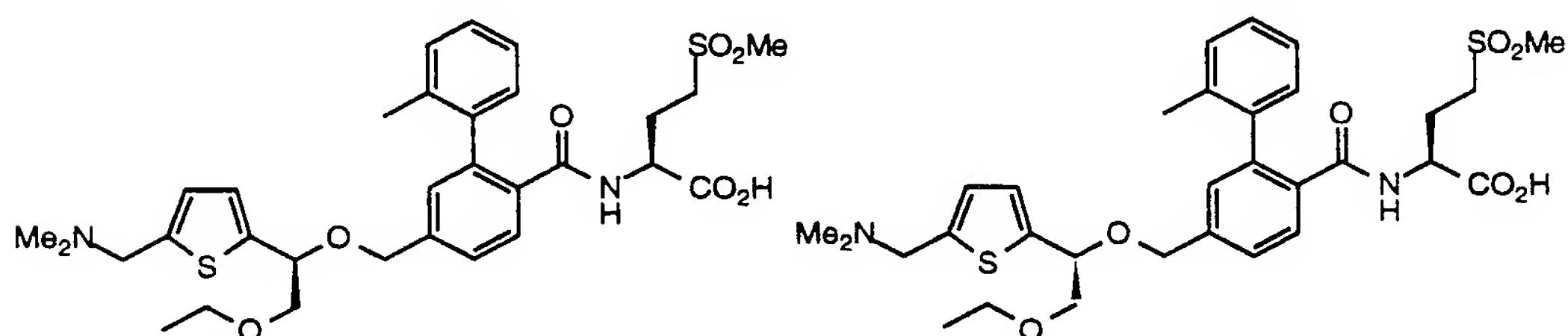
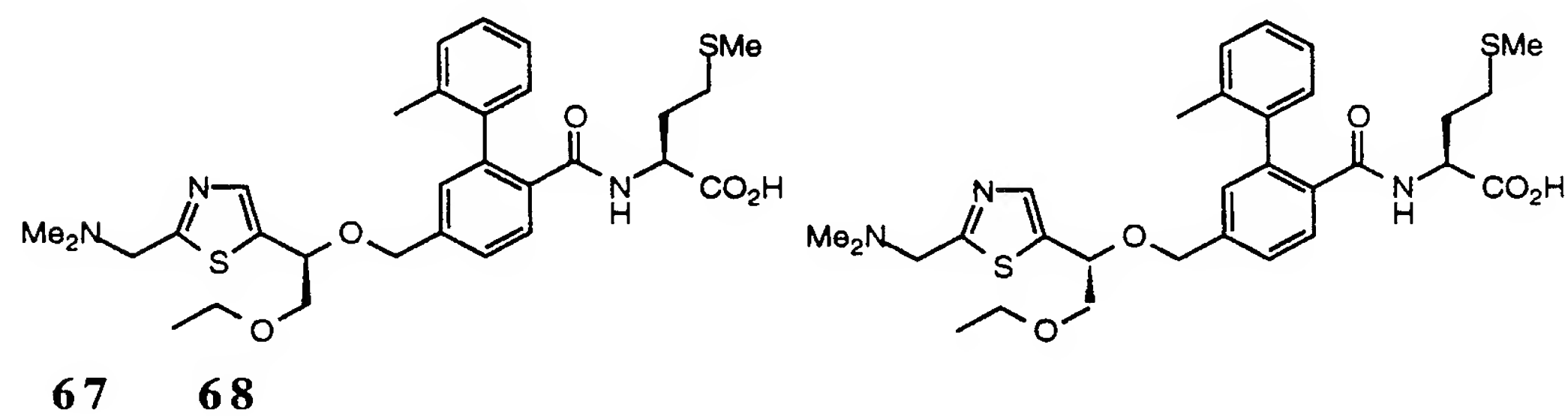
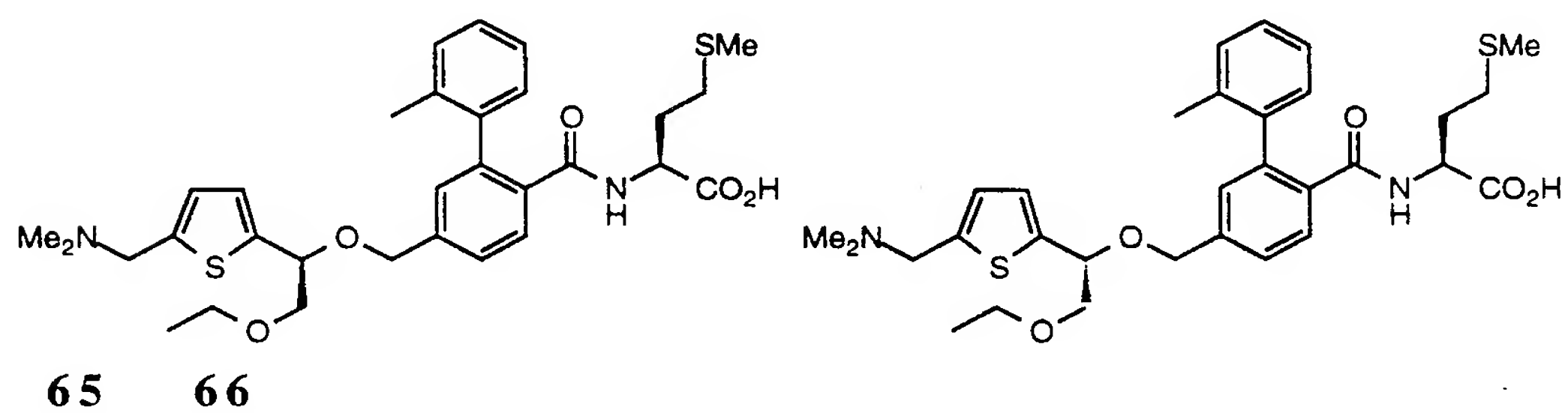
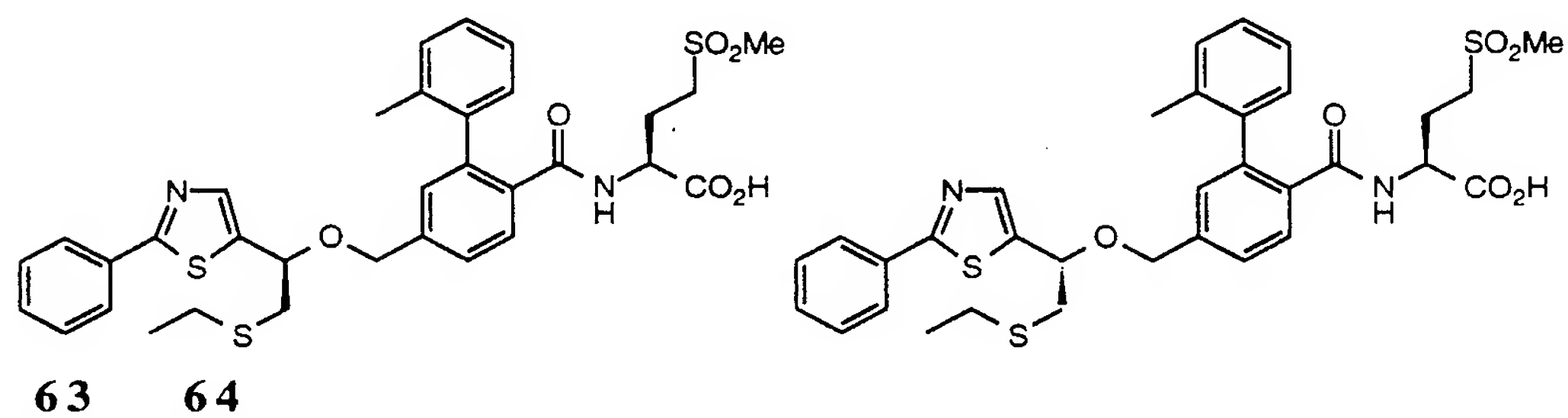
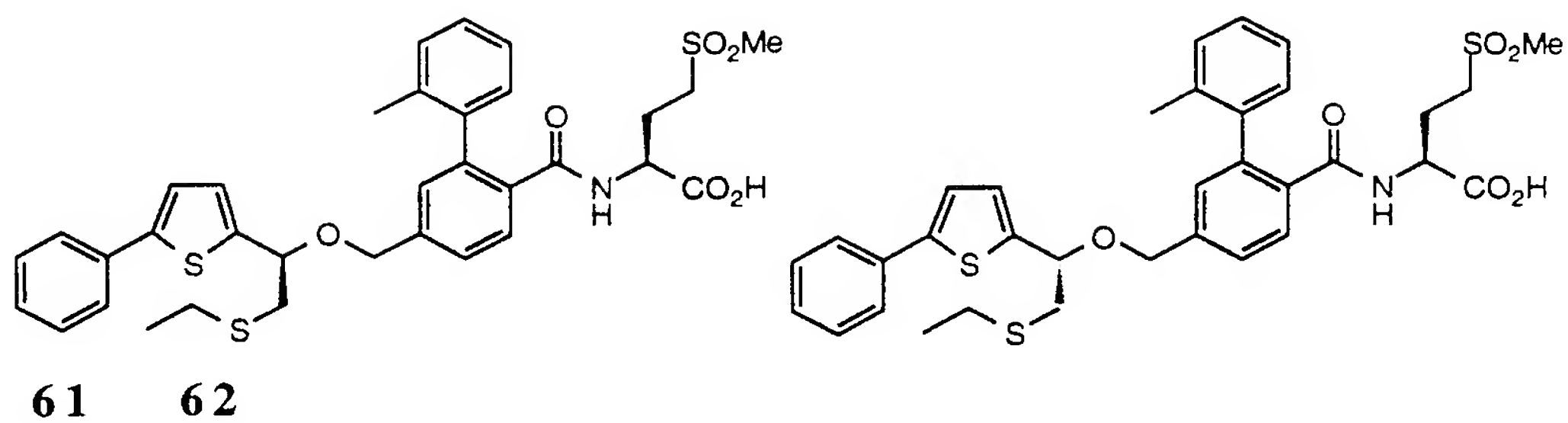


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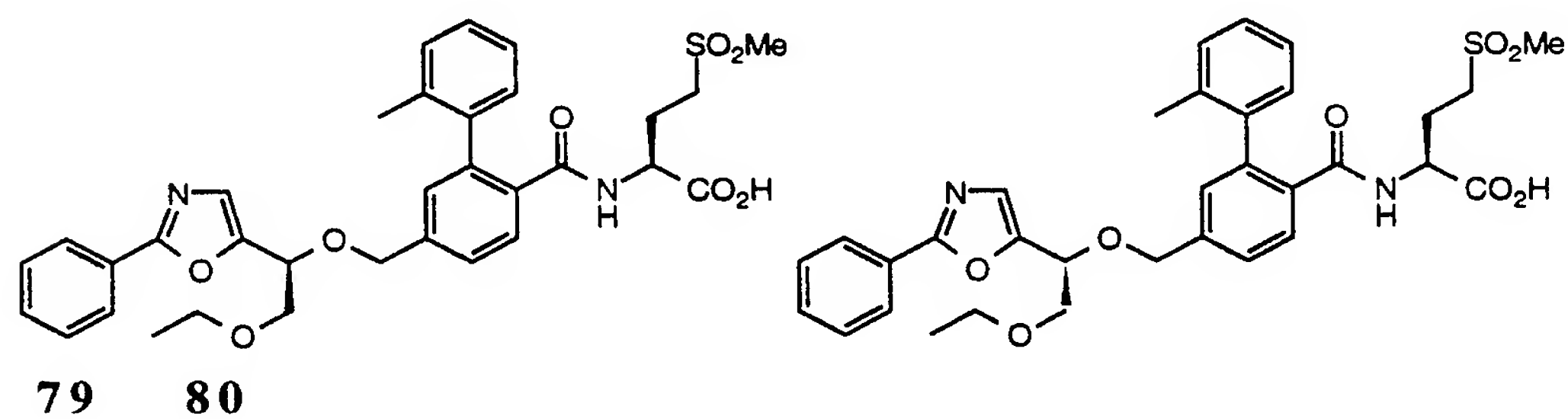
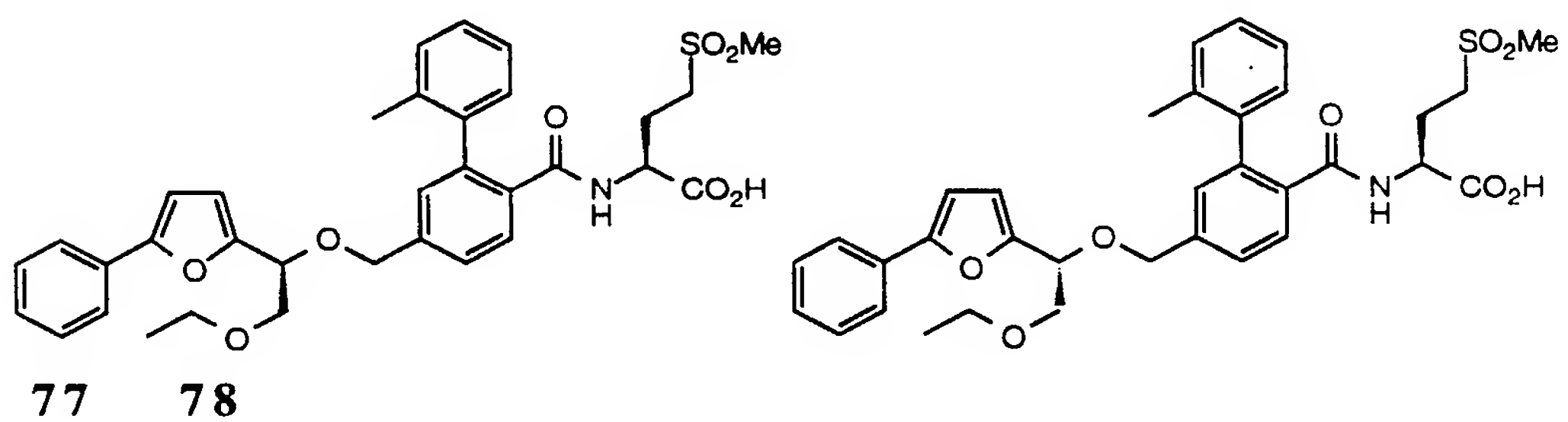
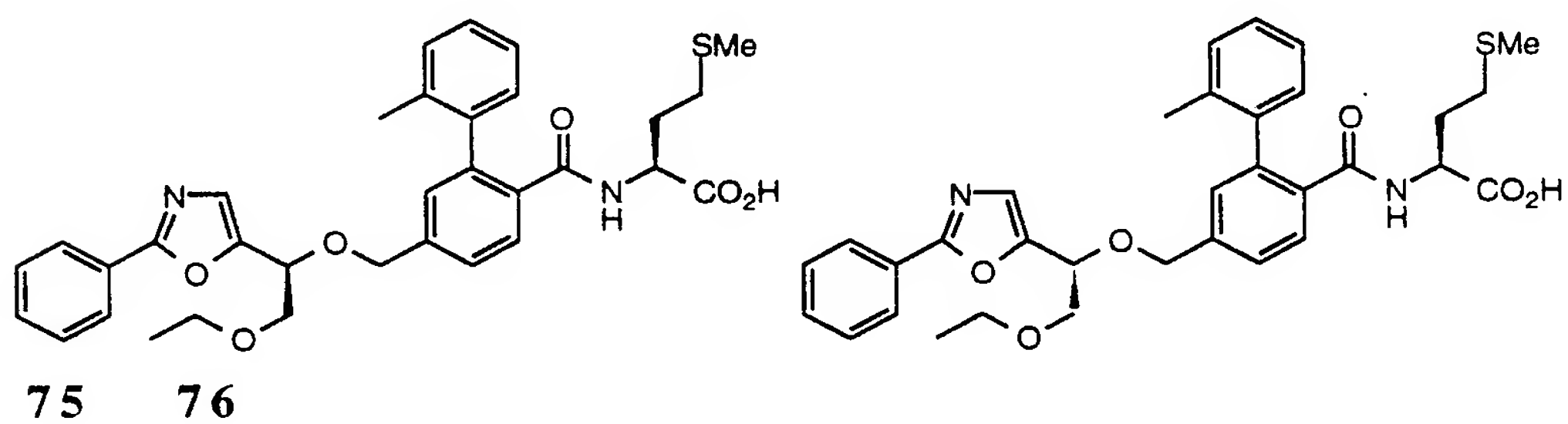
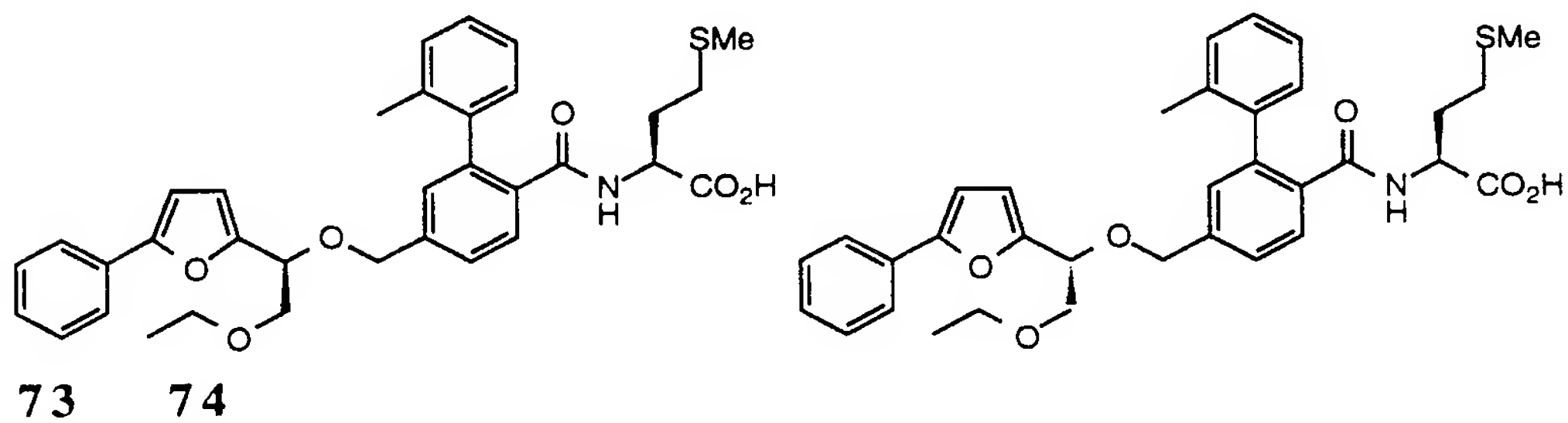
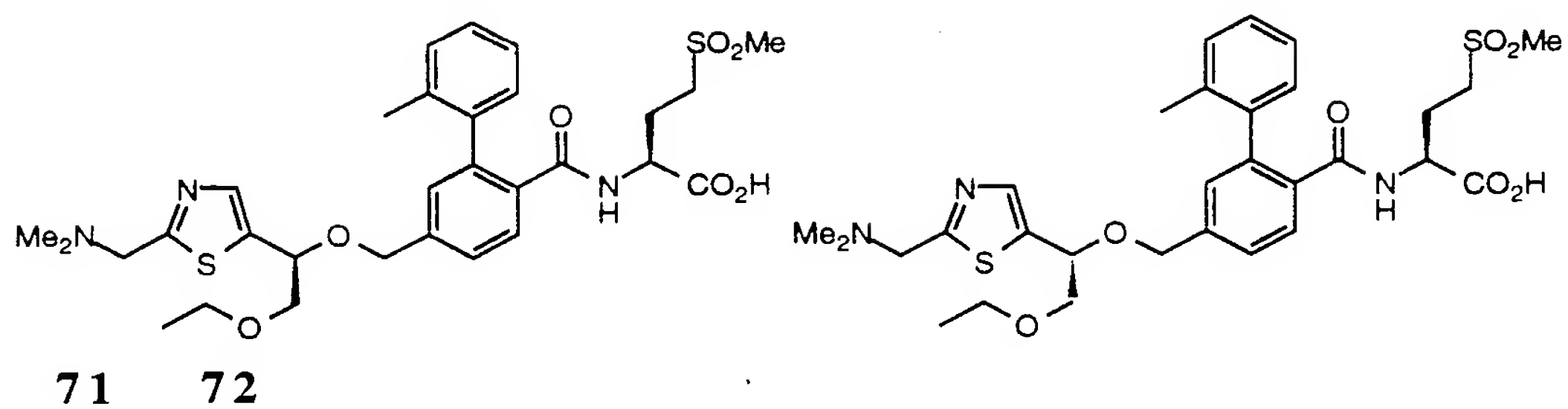


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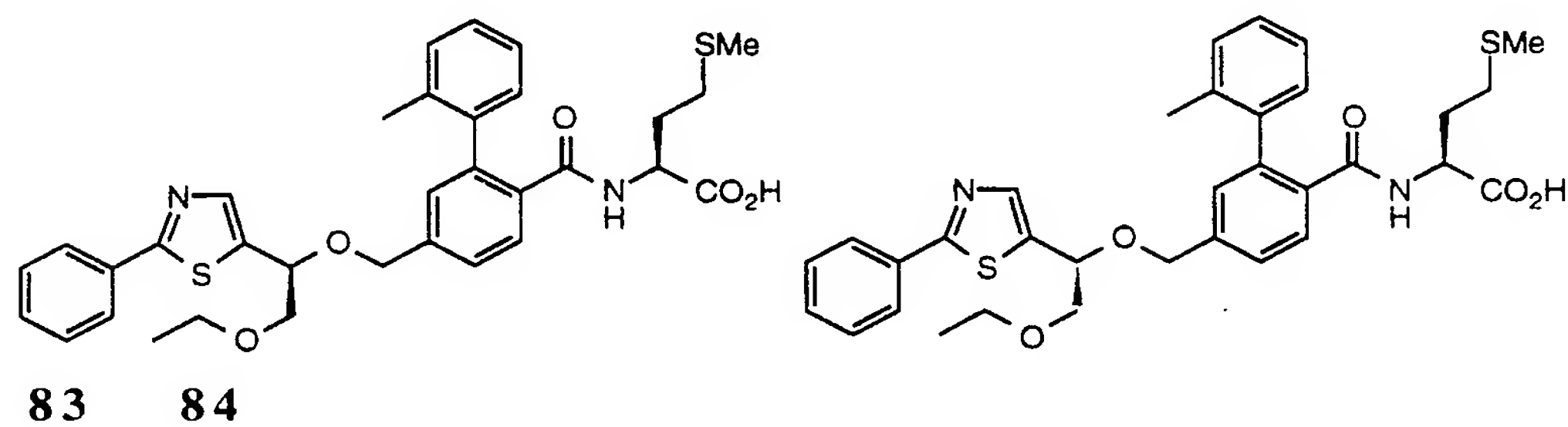
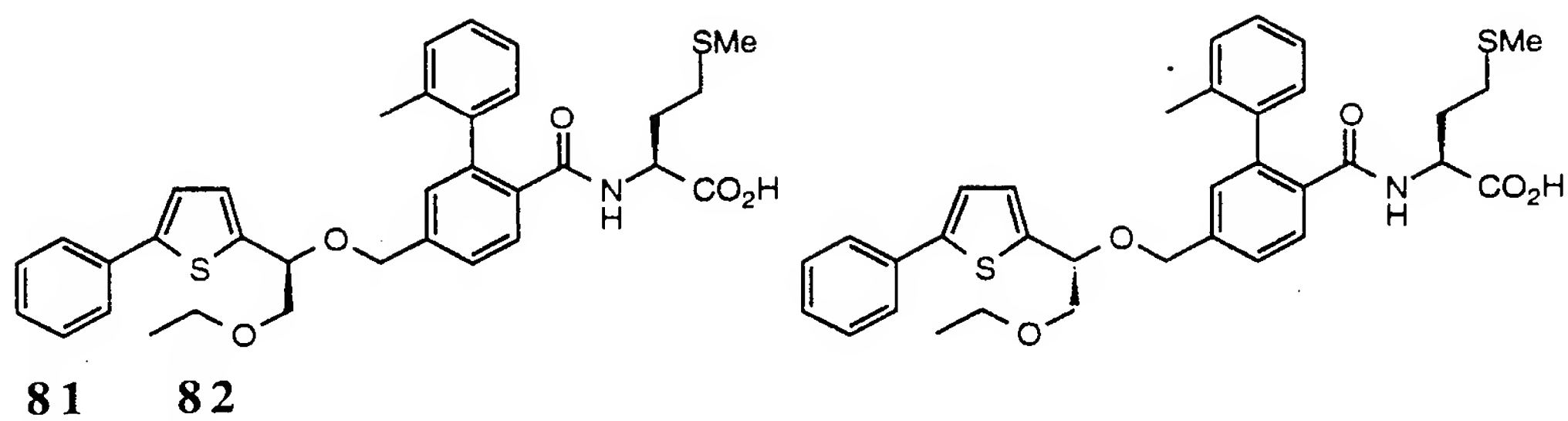


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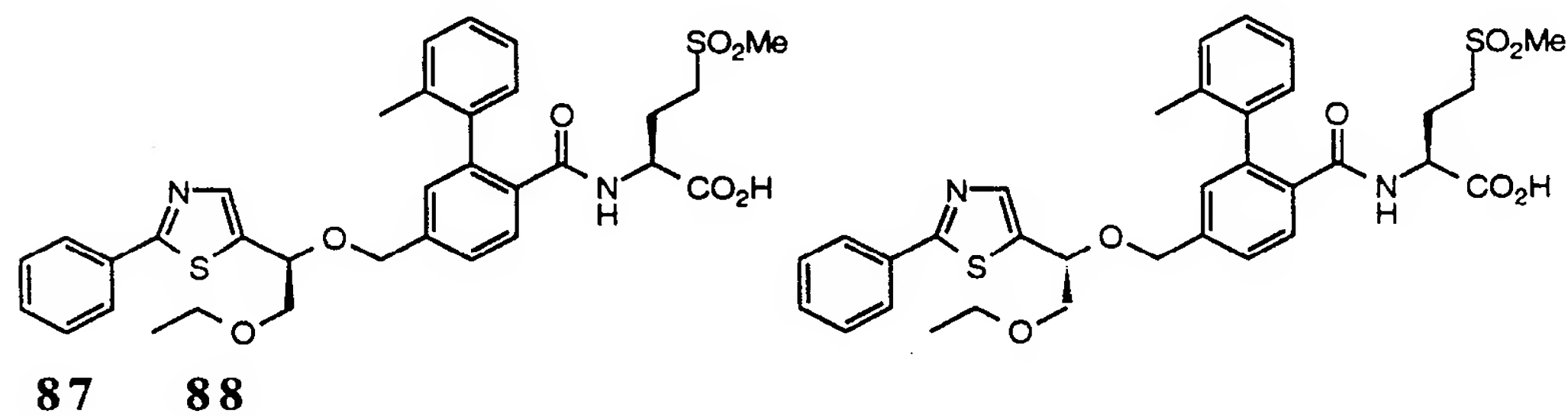
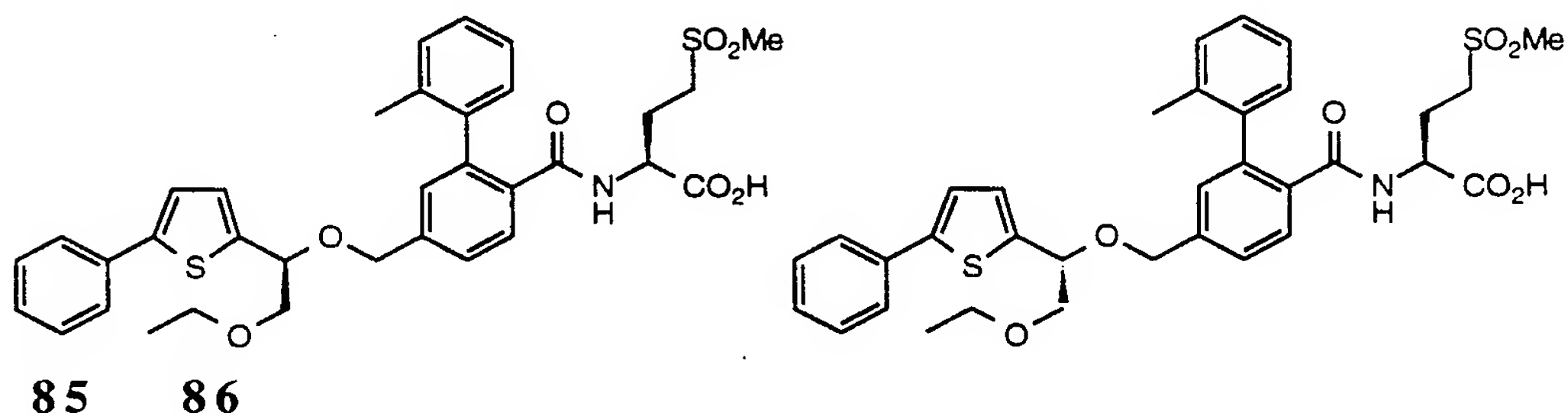




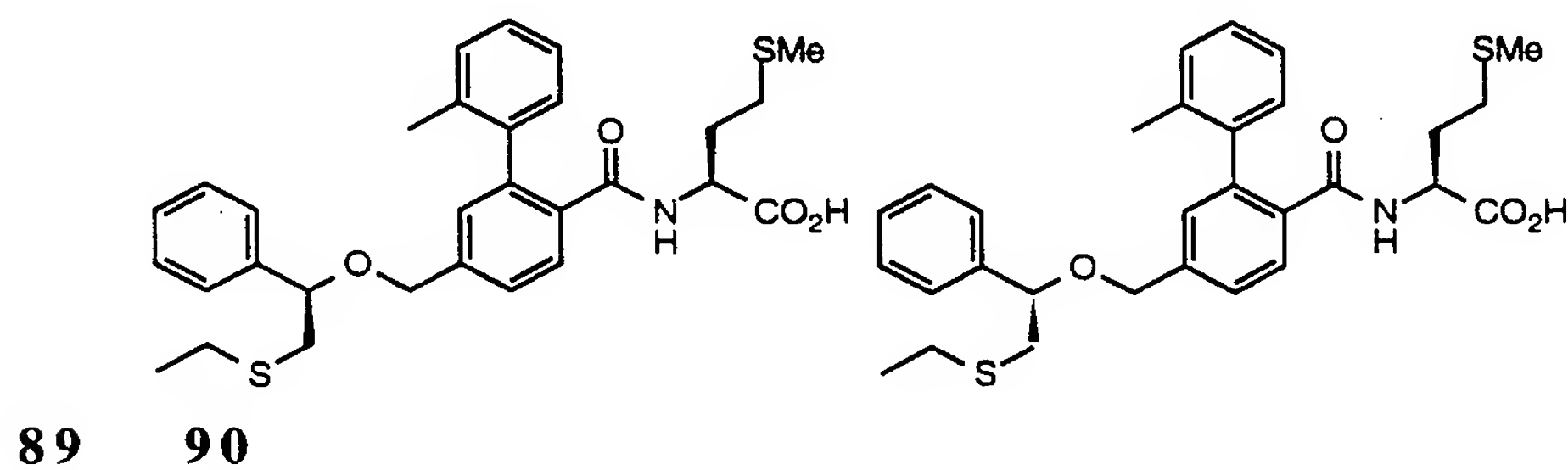
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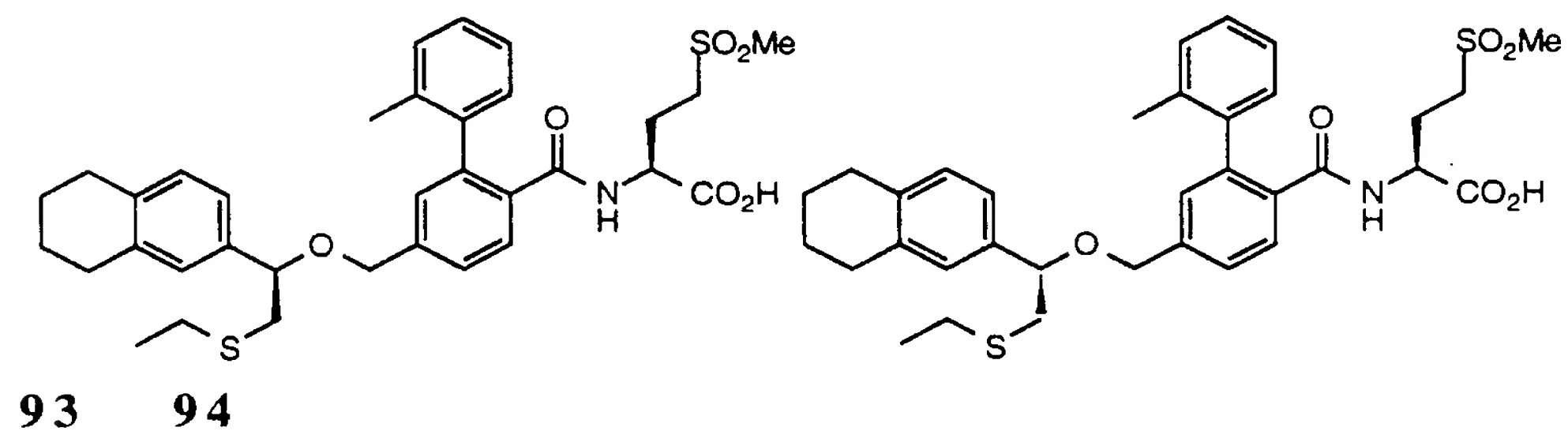
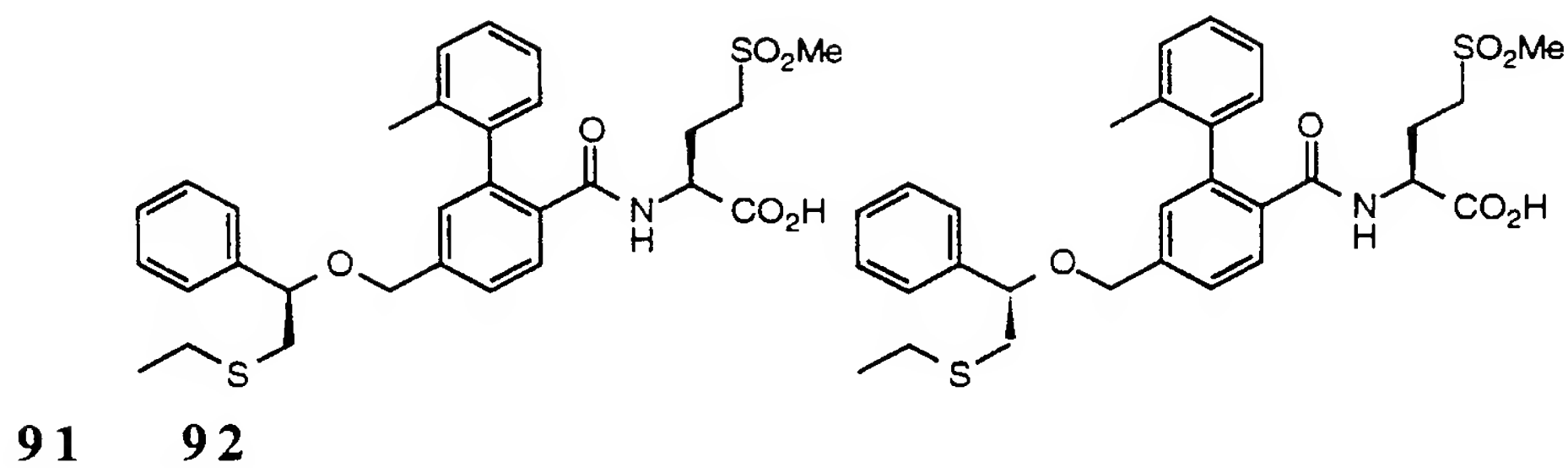
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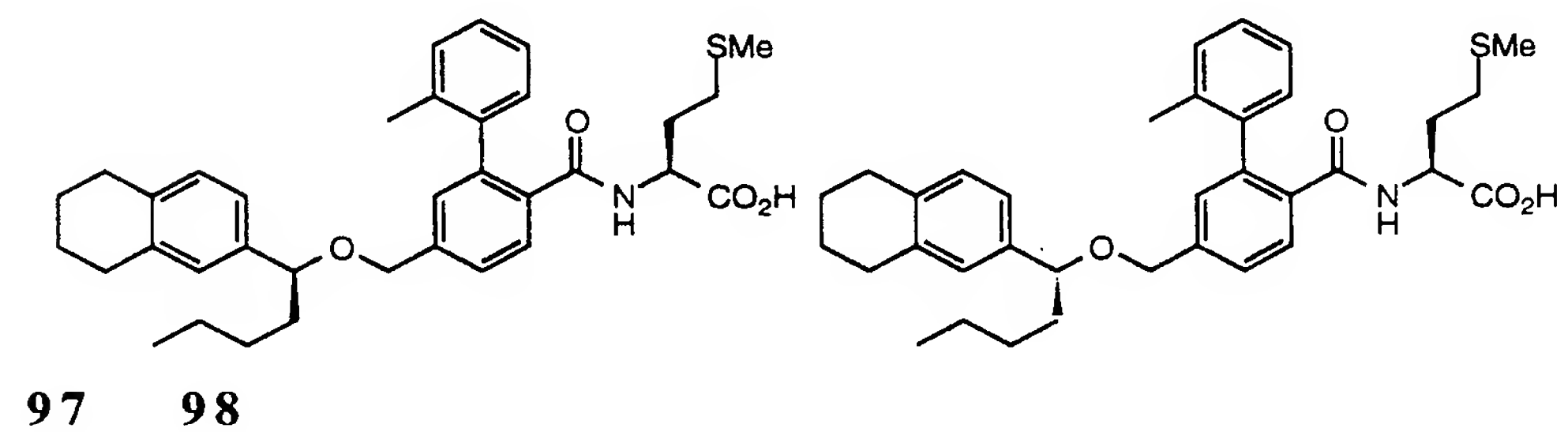
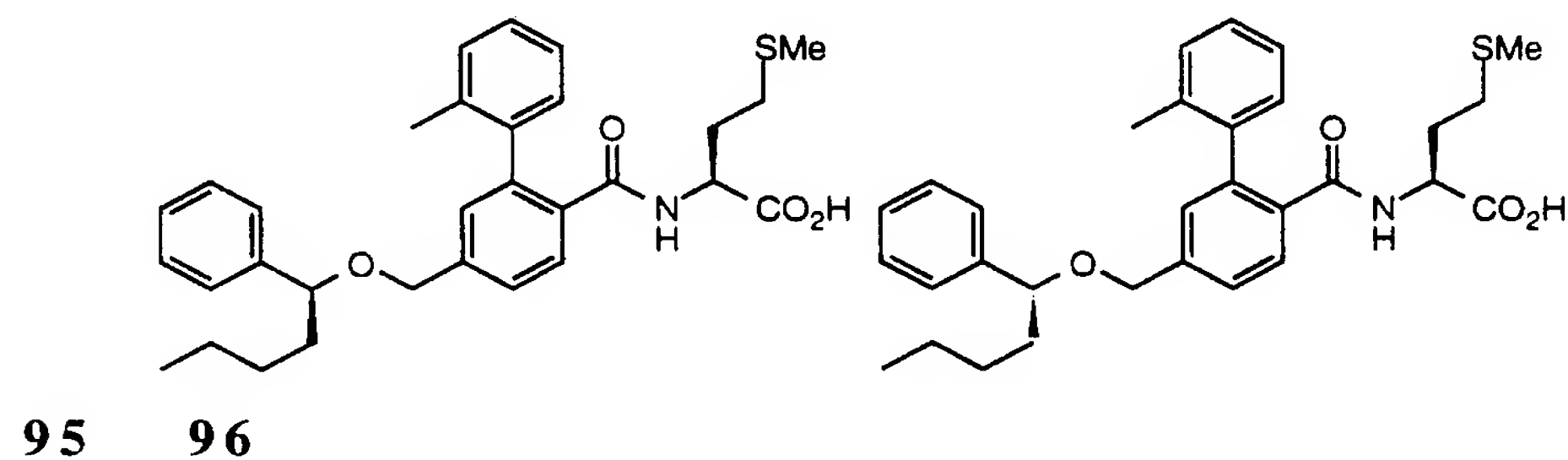
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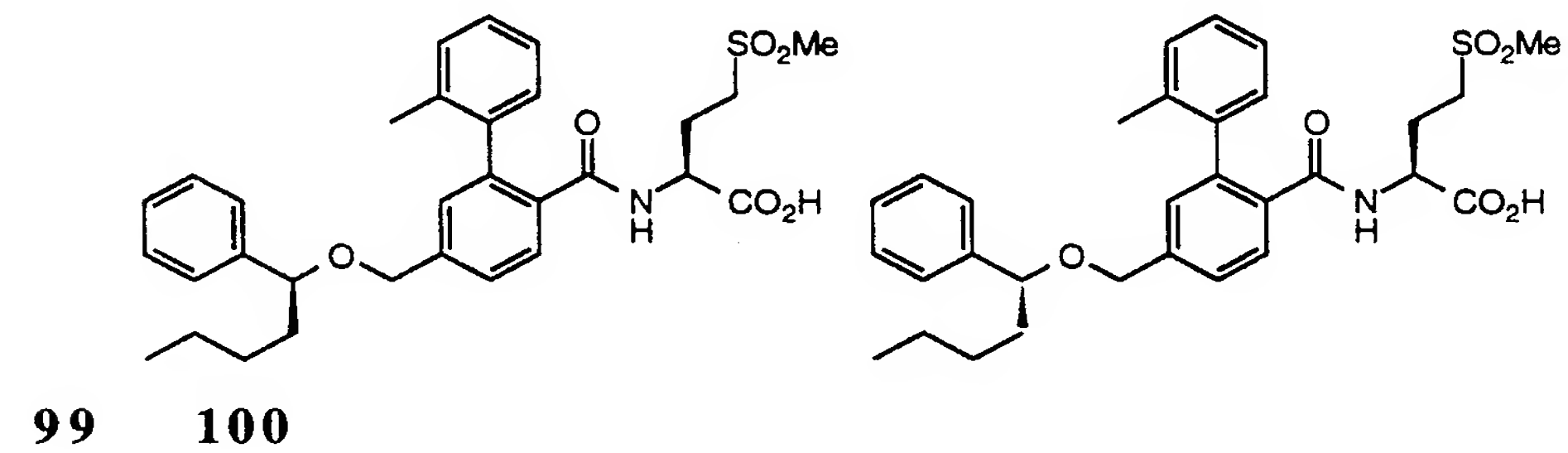
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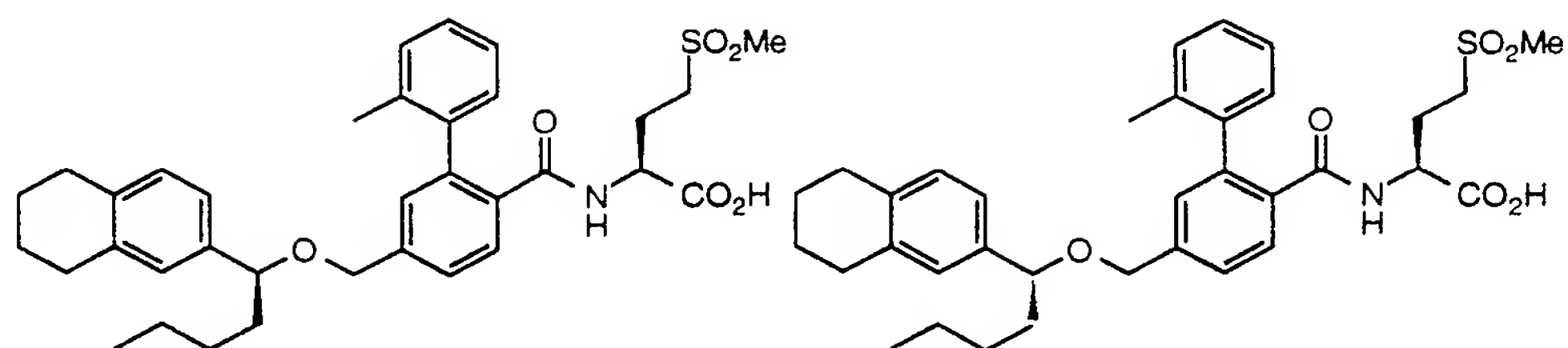


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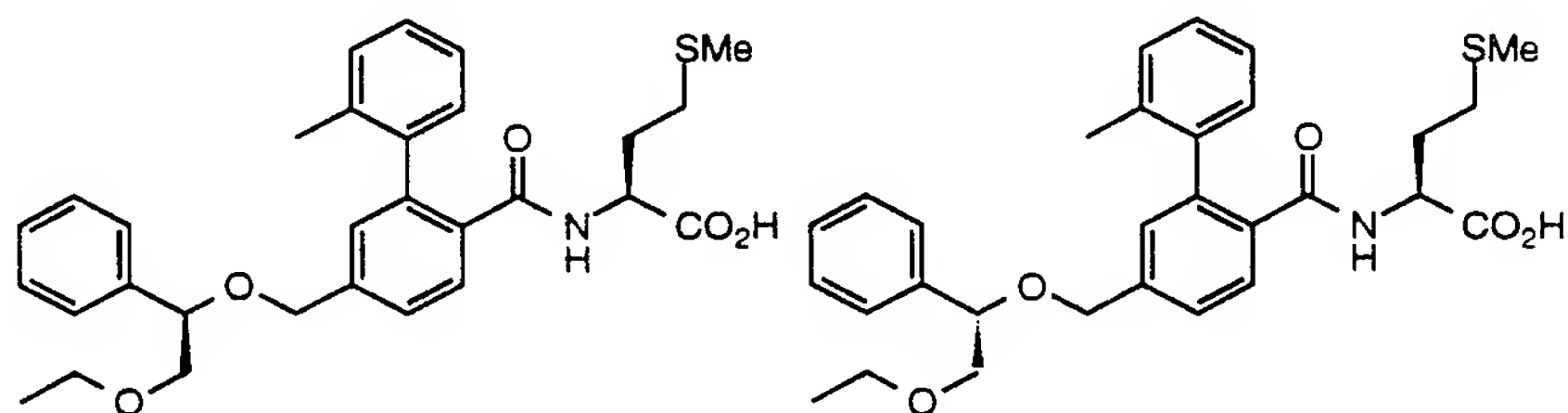
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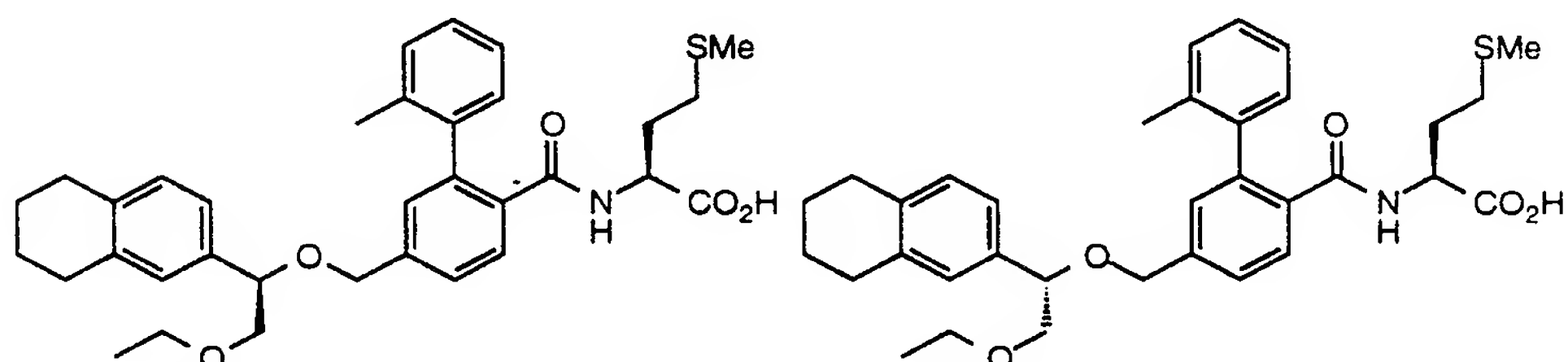


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101 102

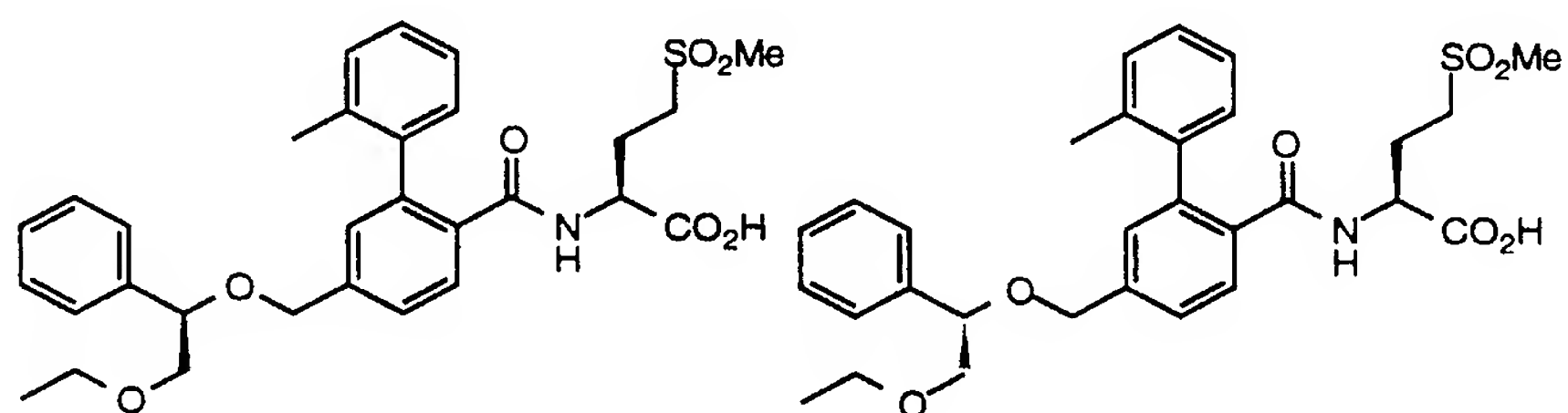


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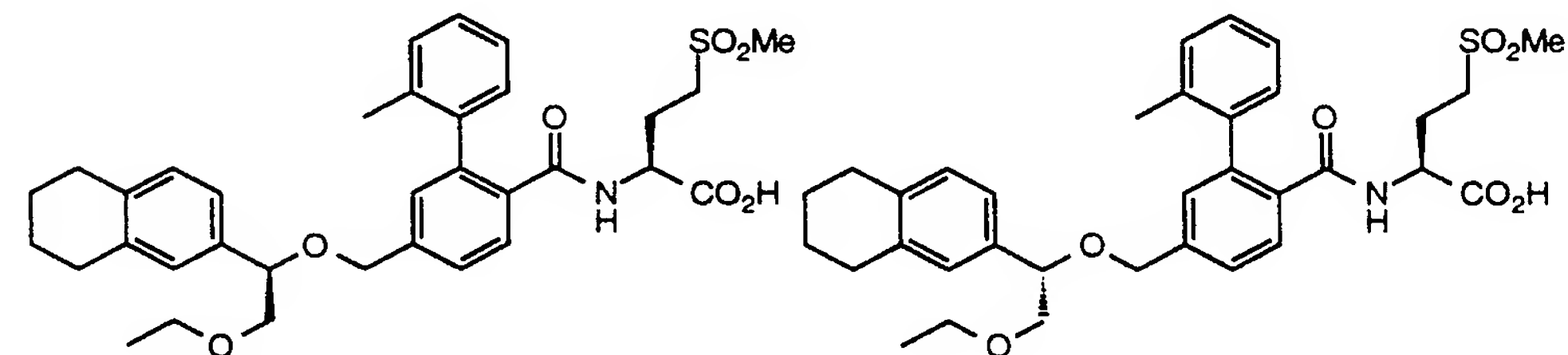
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105 106



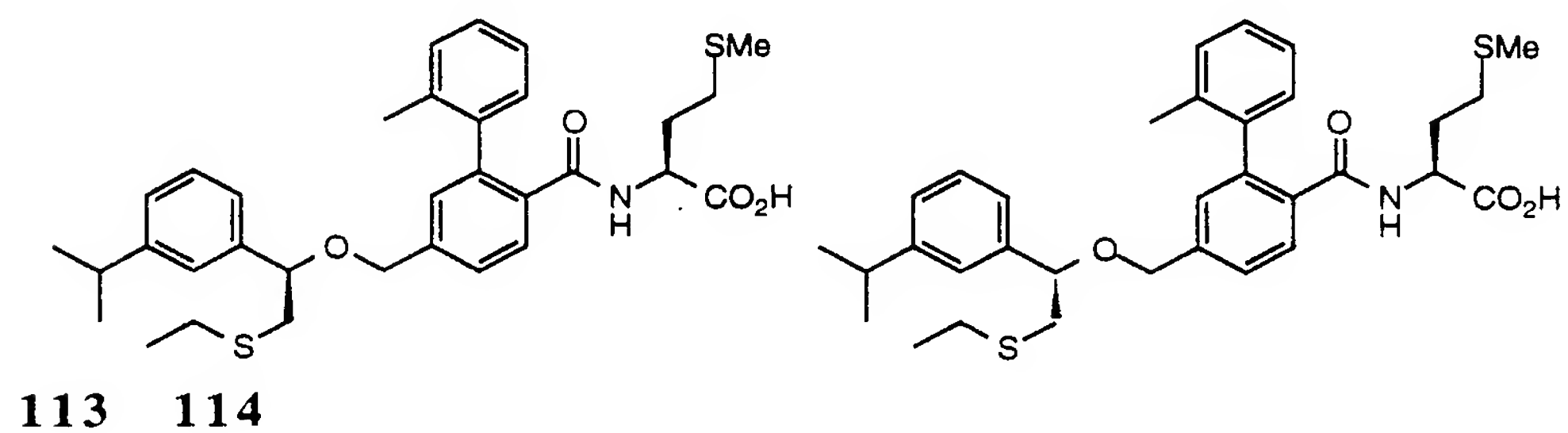
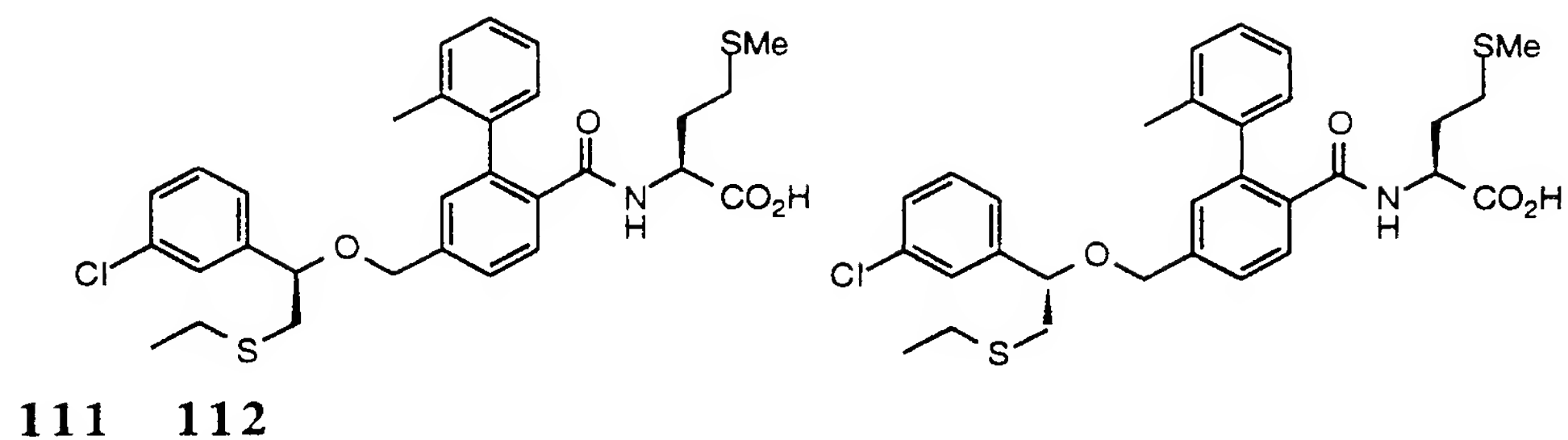
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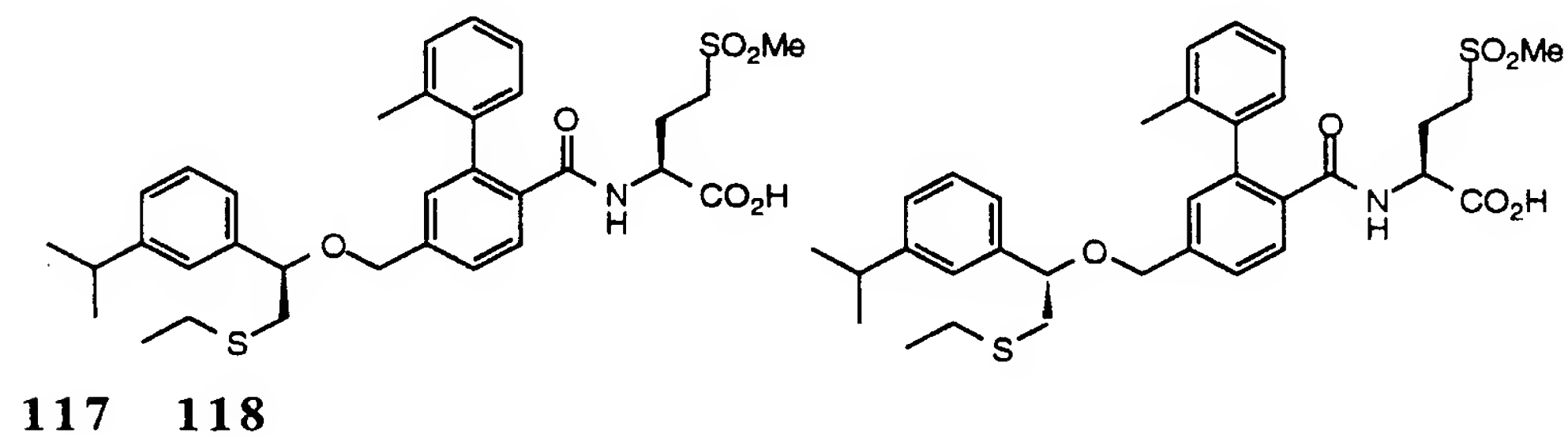
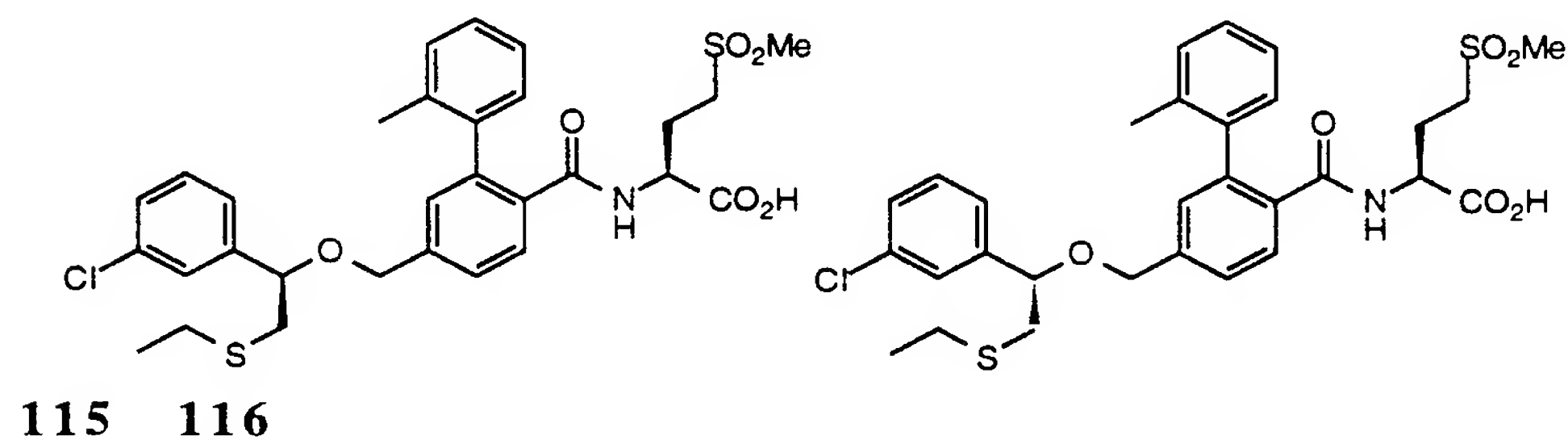


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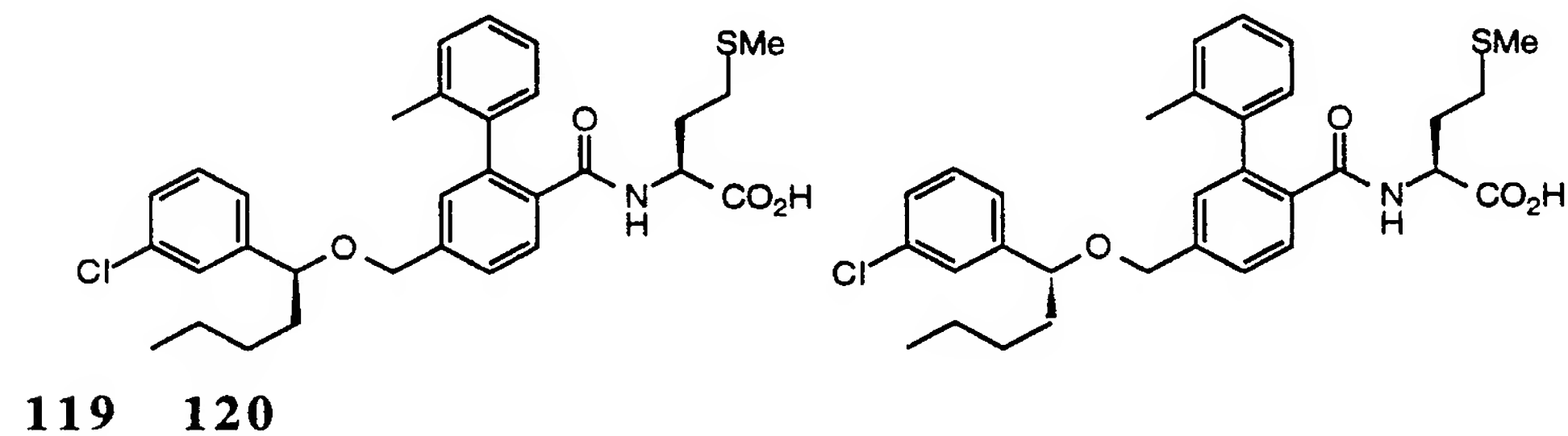
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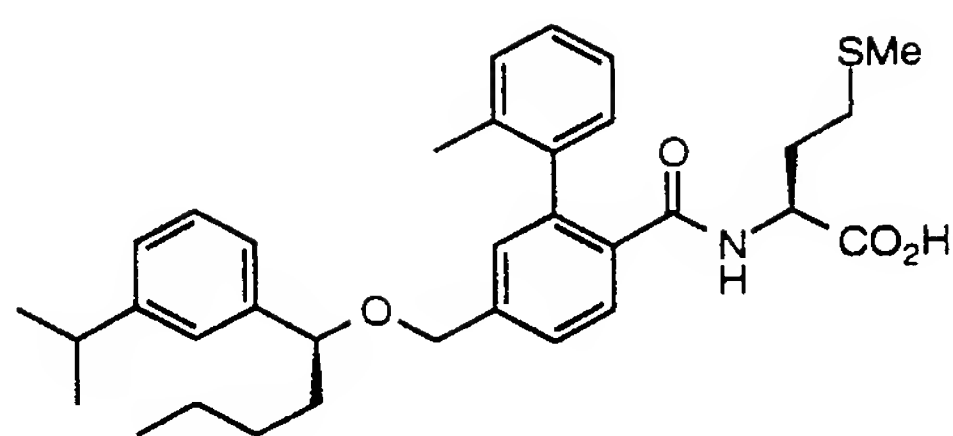


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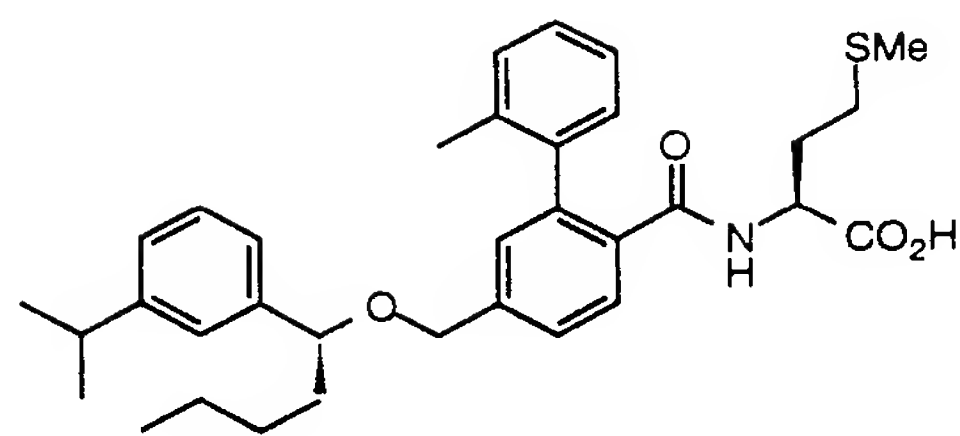


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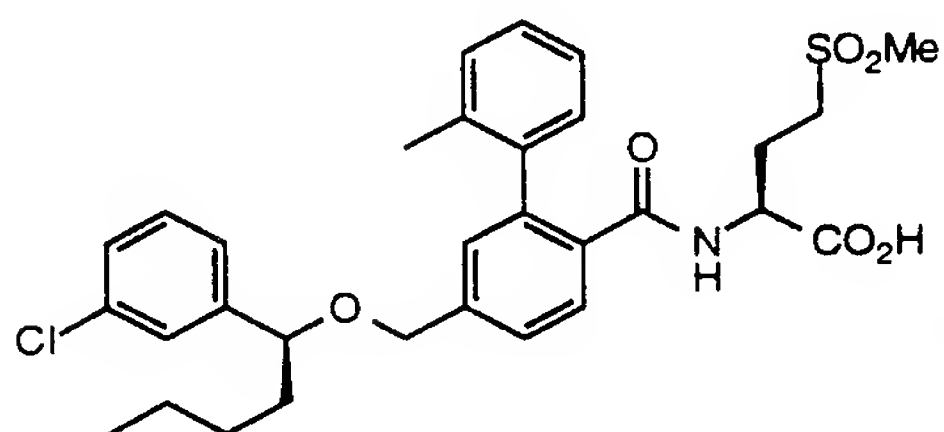




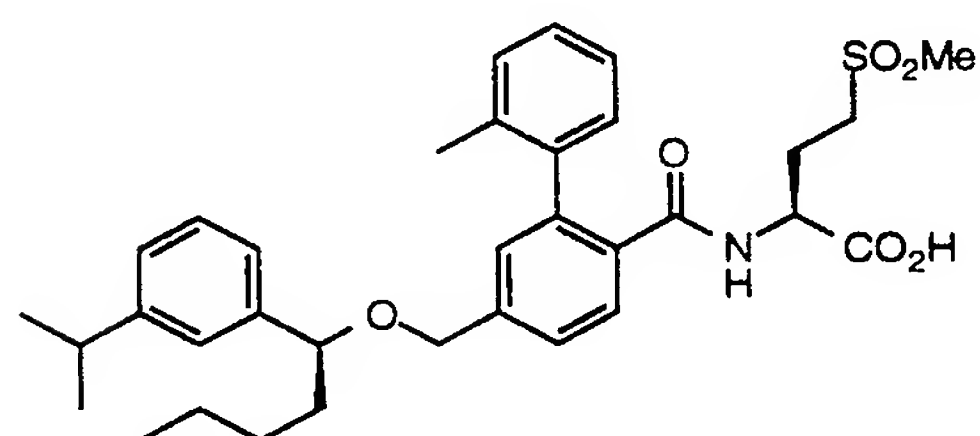
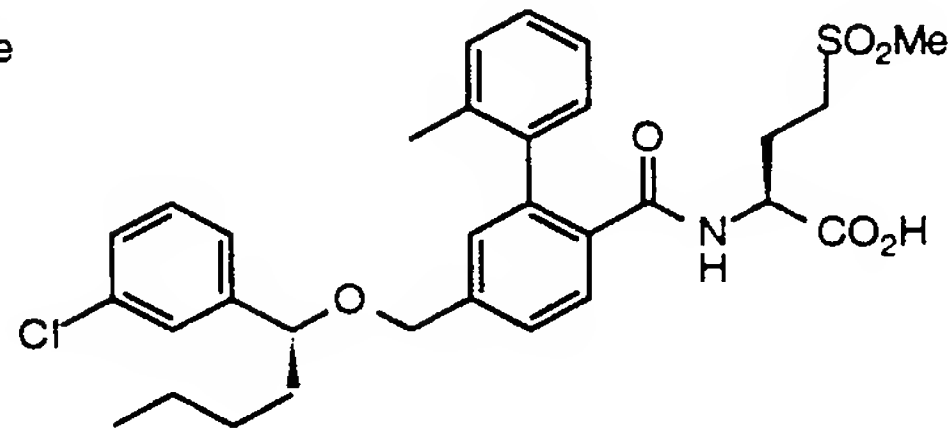
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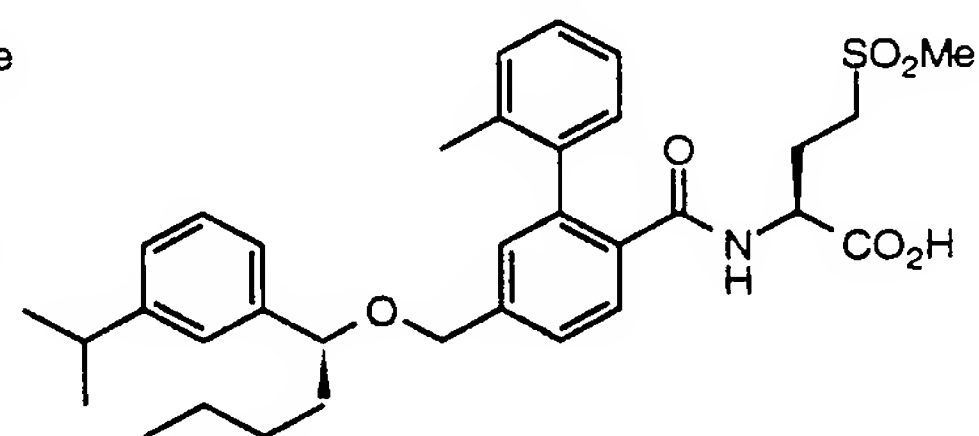
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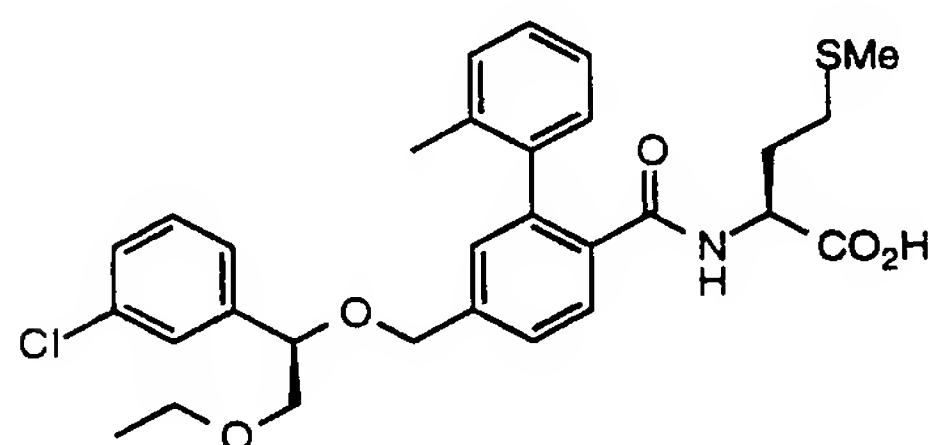
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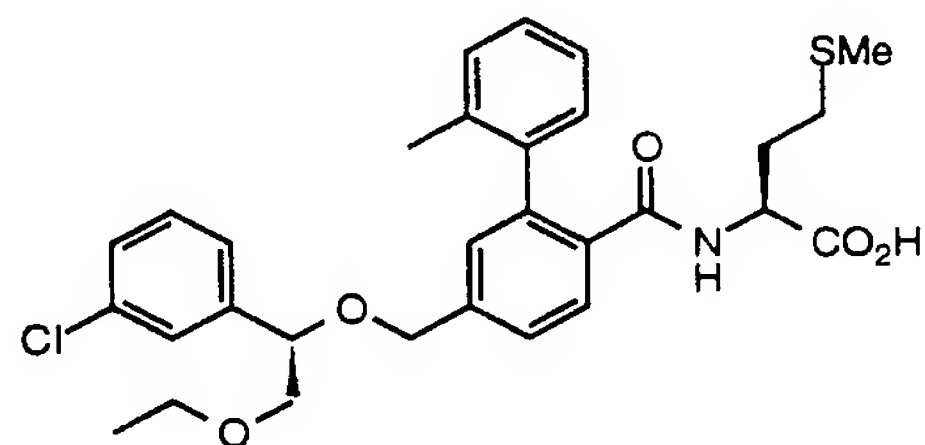
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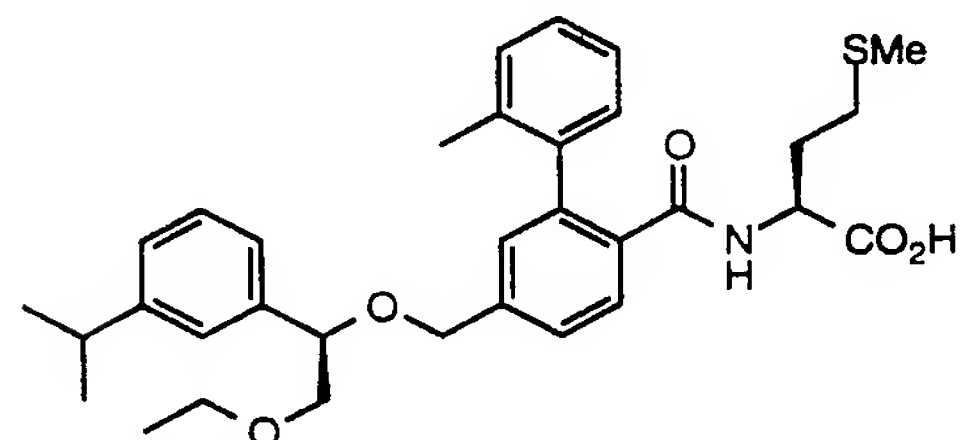
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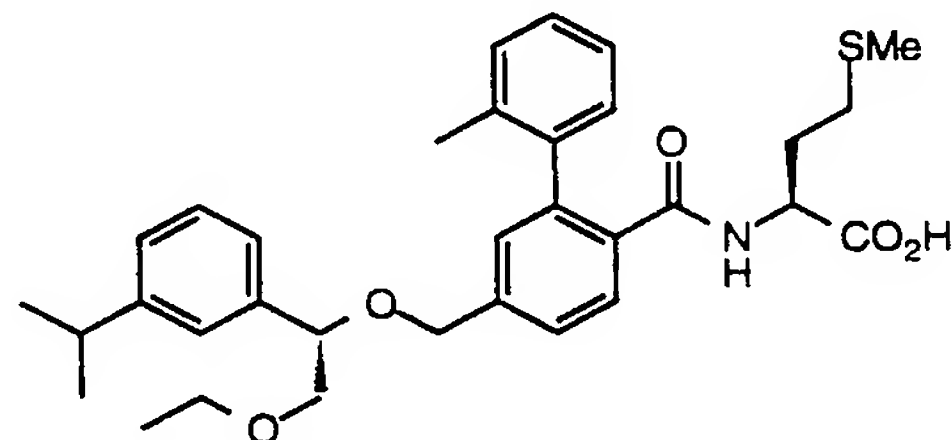
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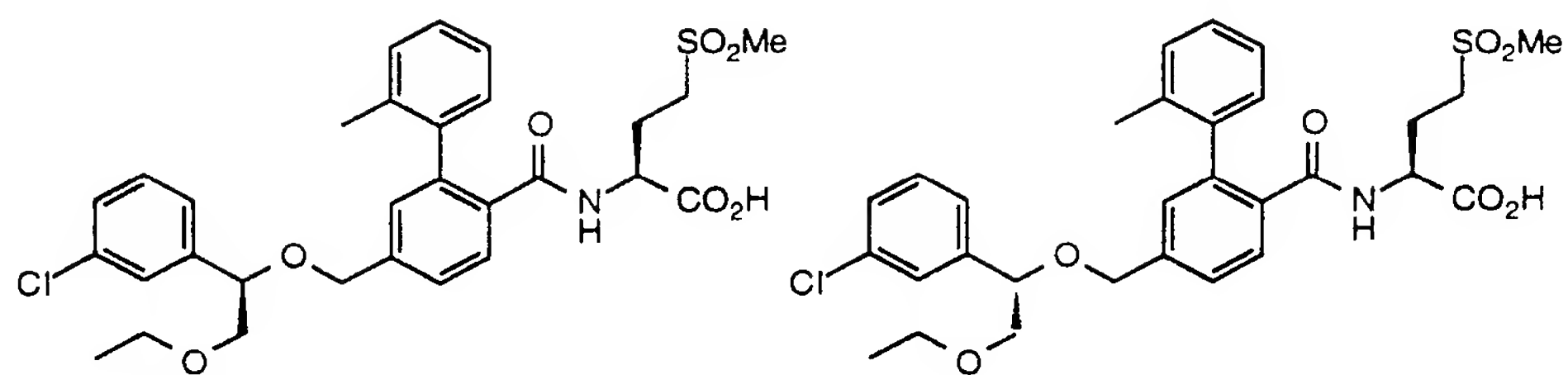


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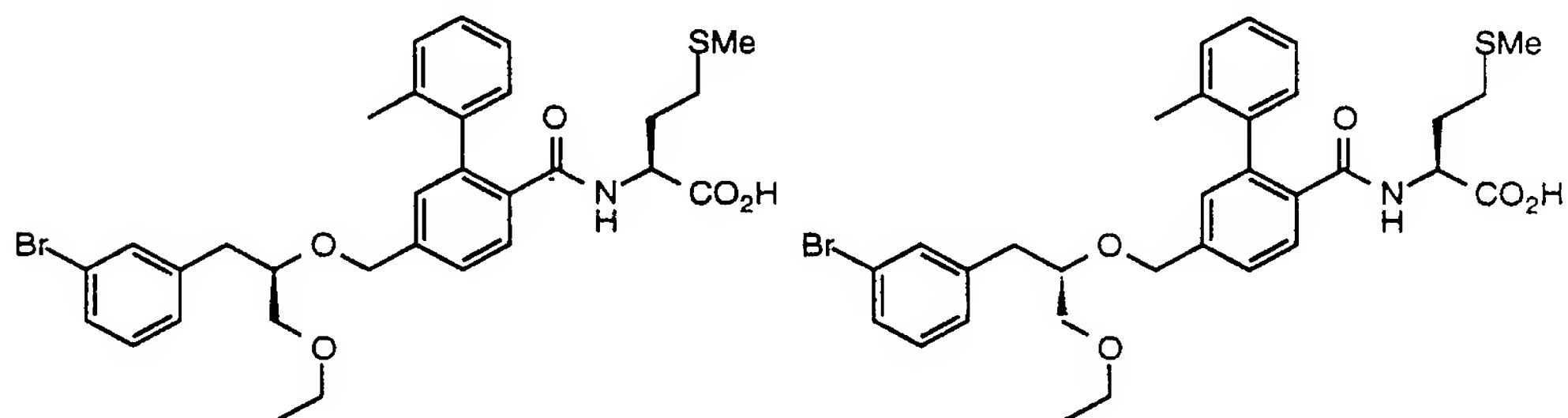
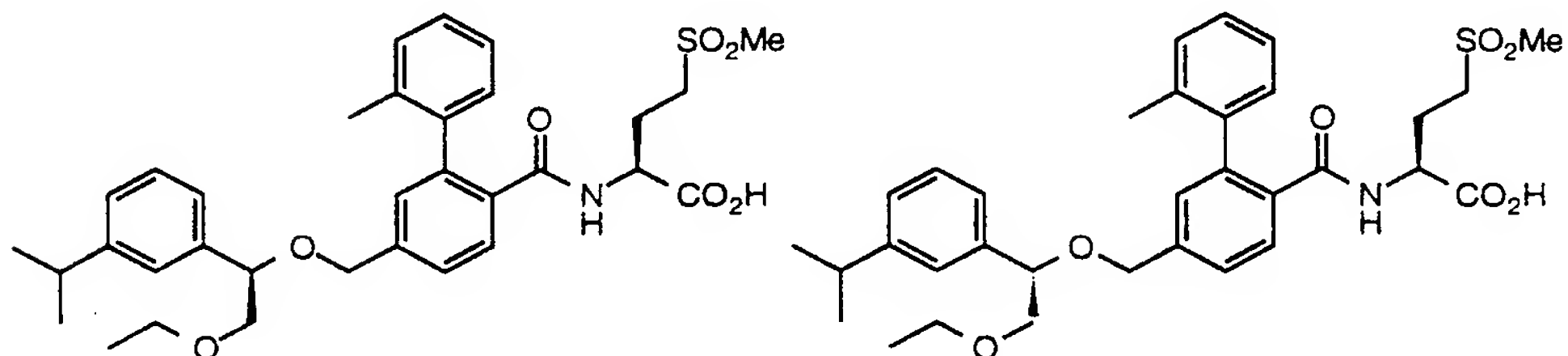


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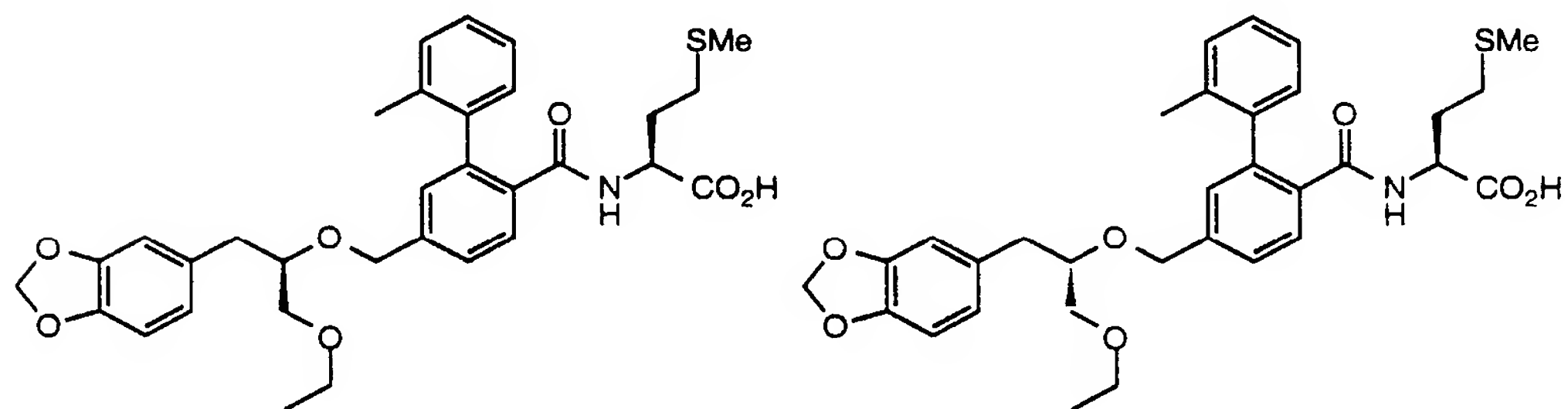




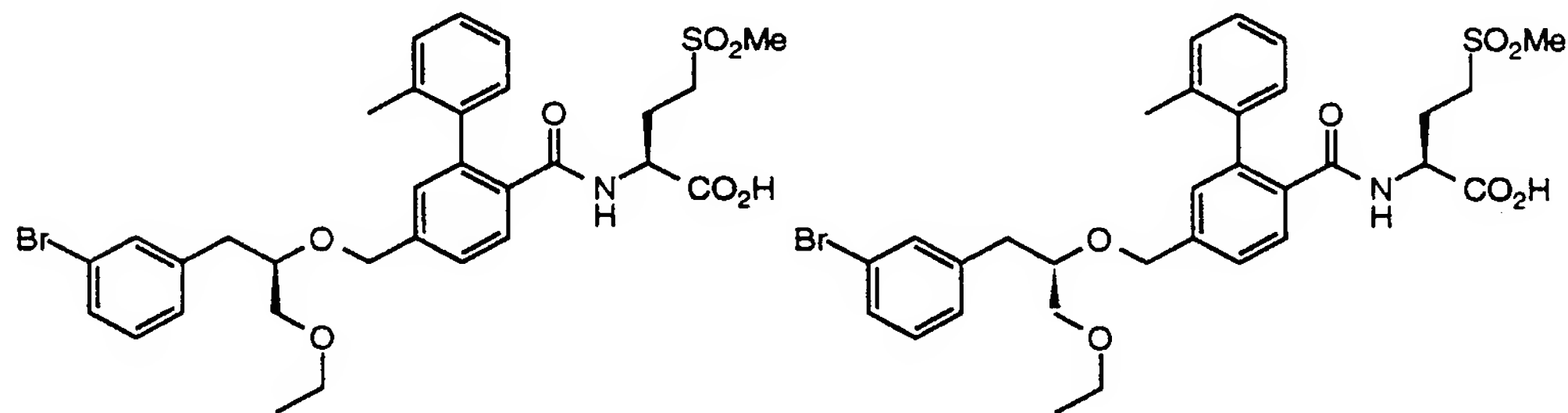
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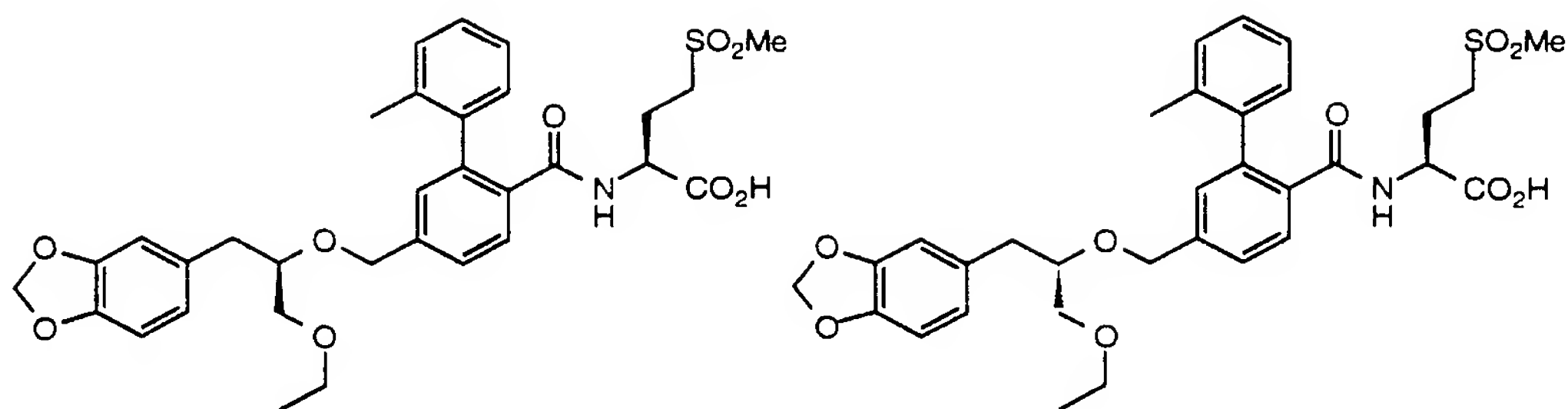
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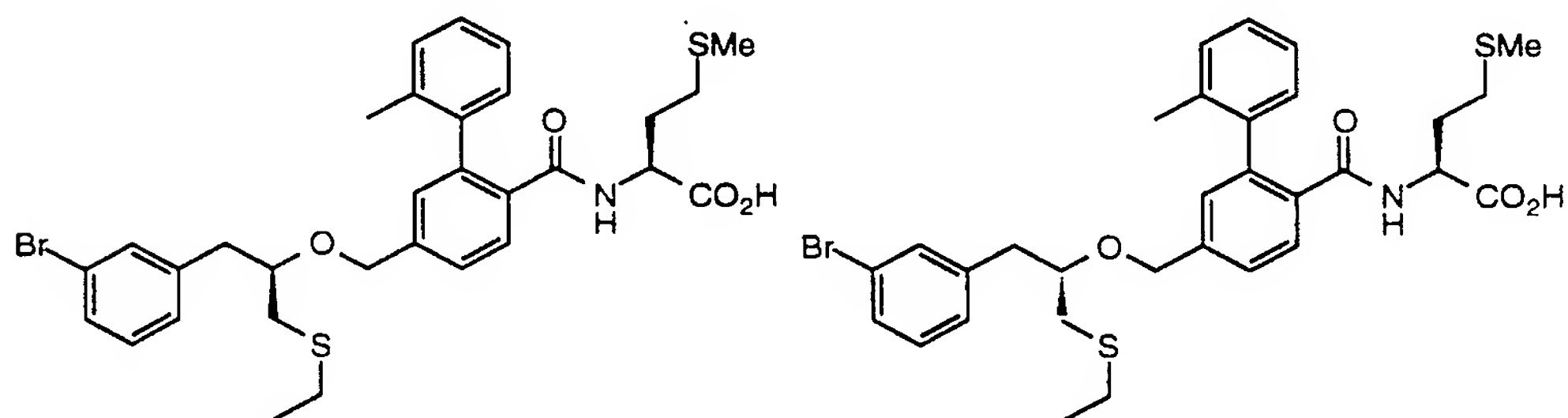


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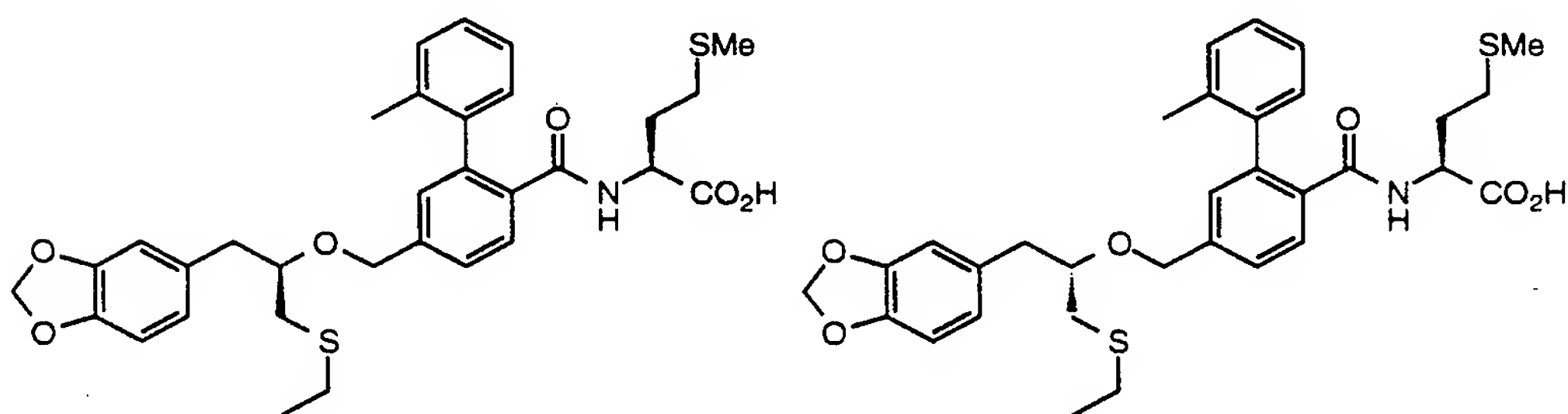


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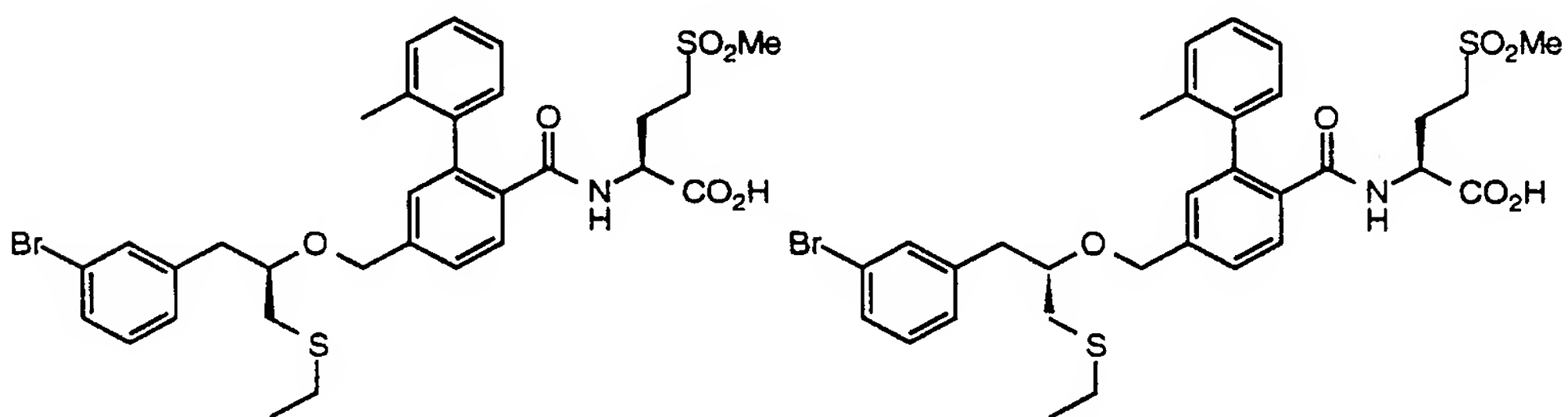


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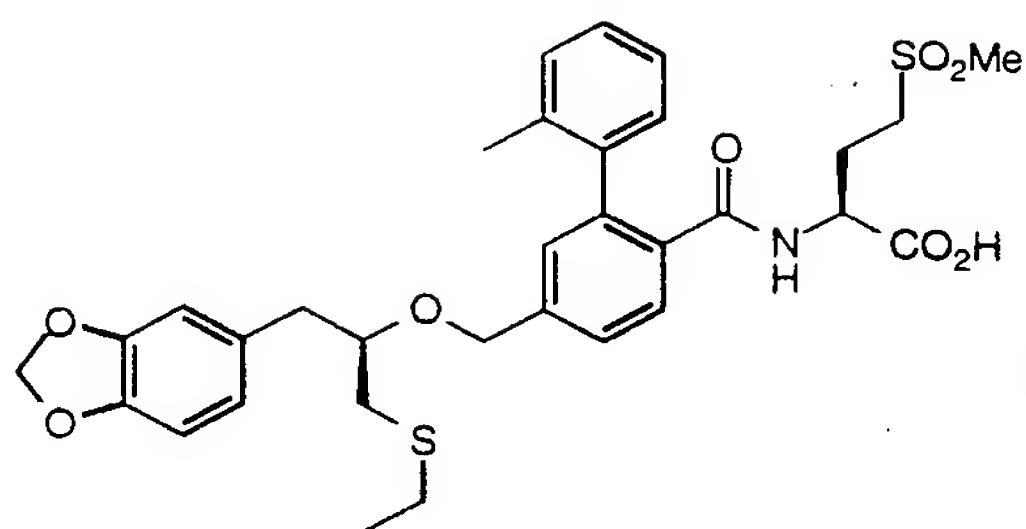
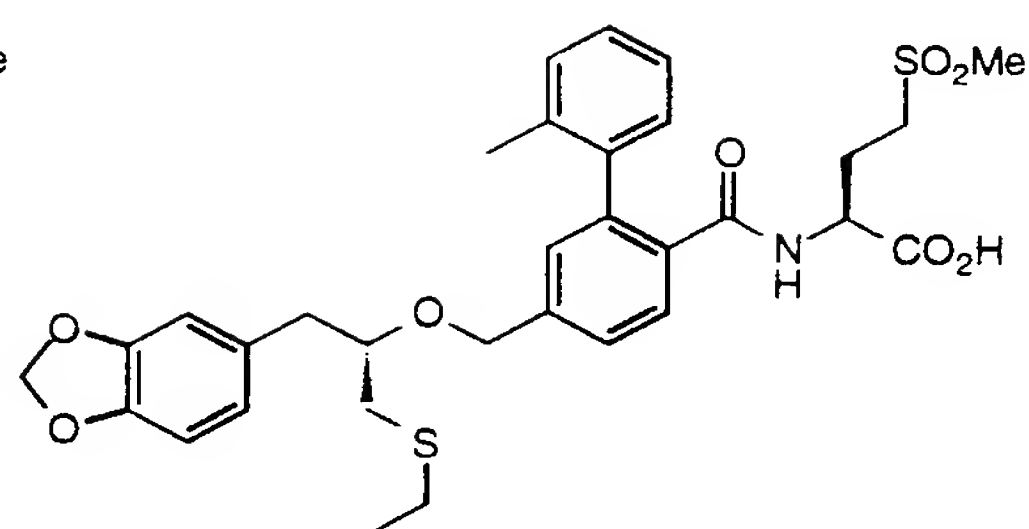
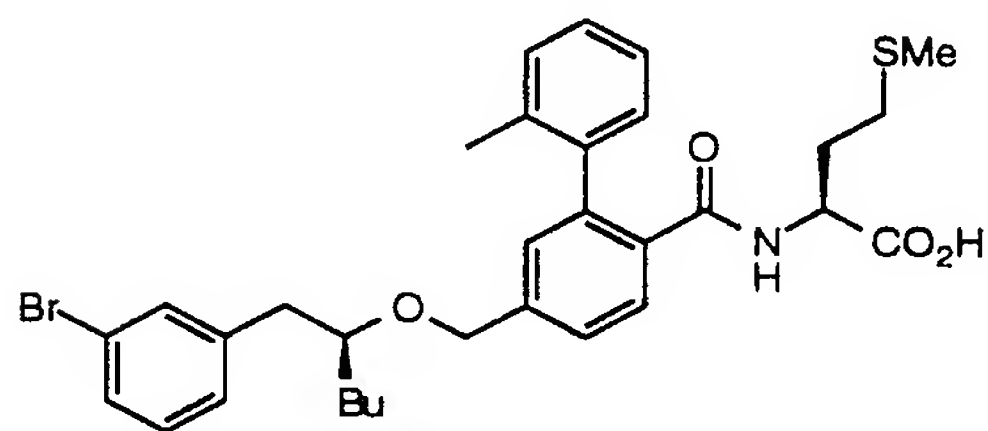
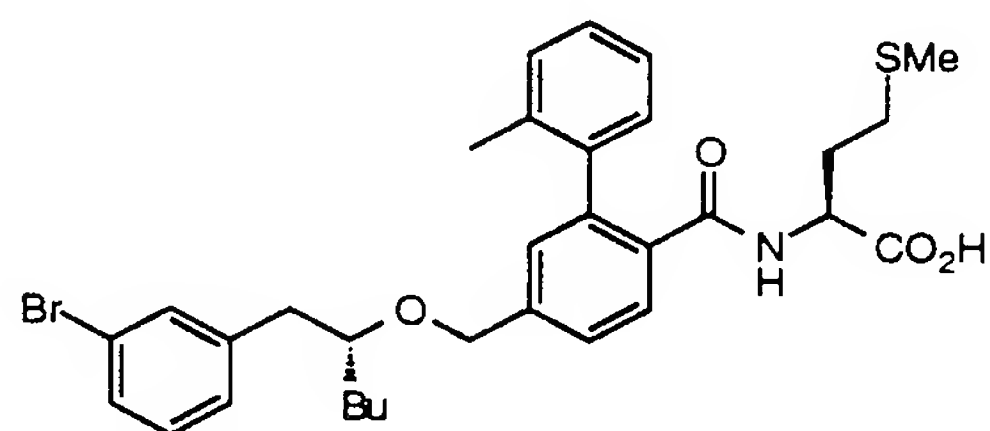
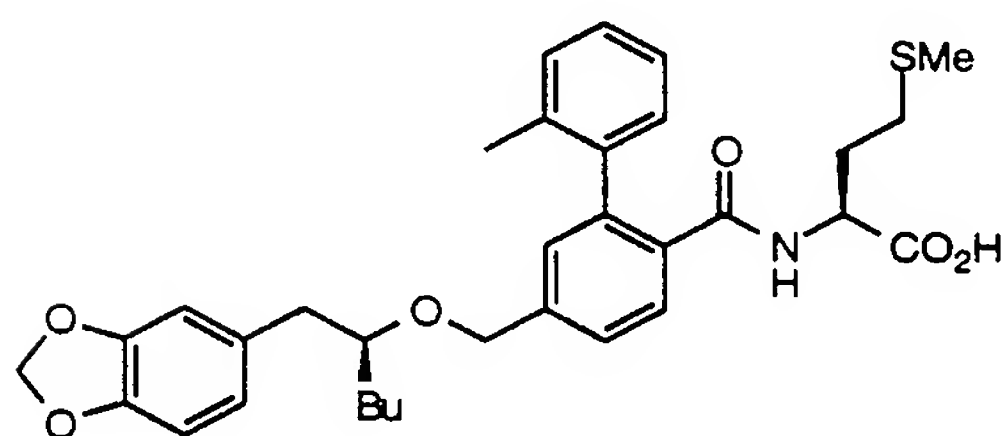
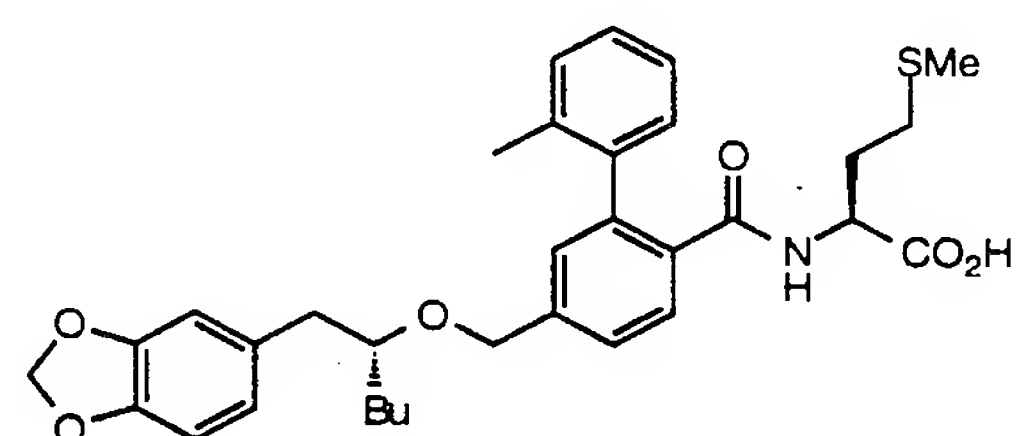
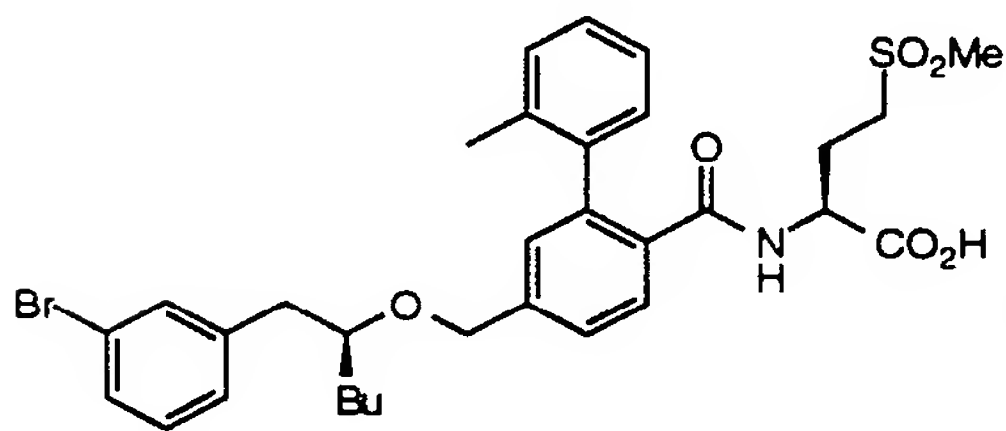
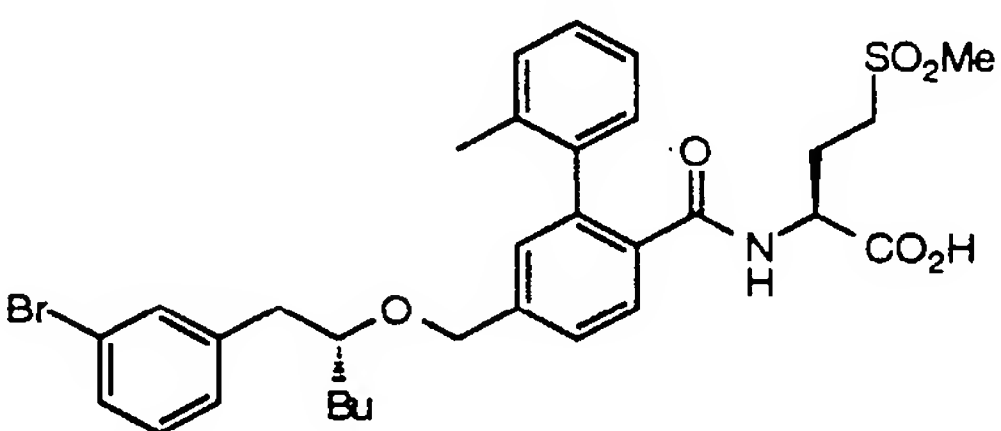
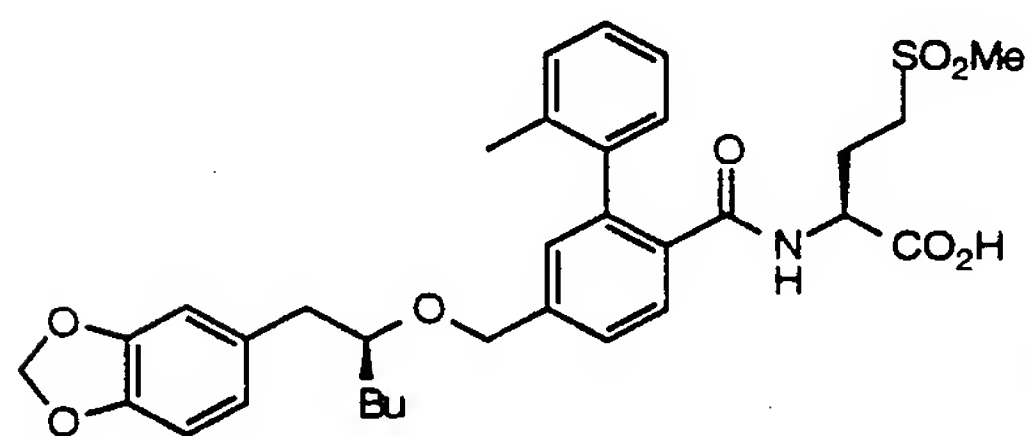
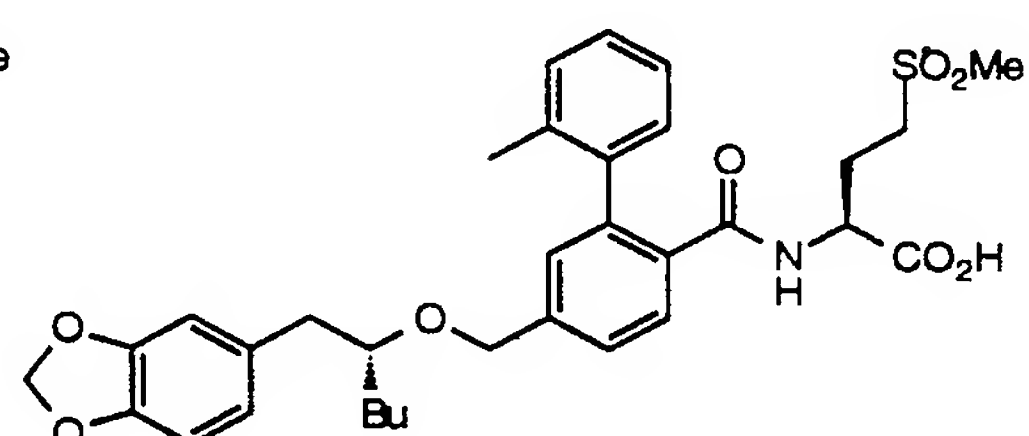
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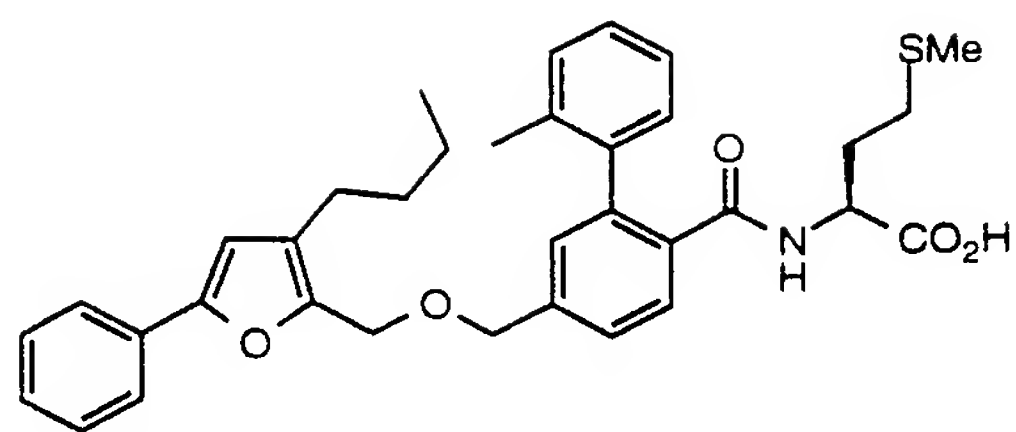


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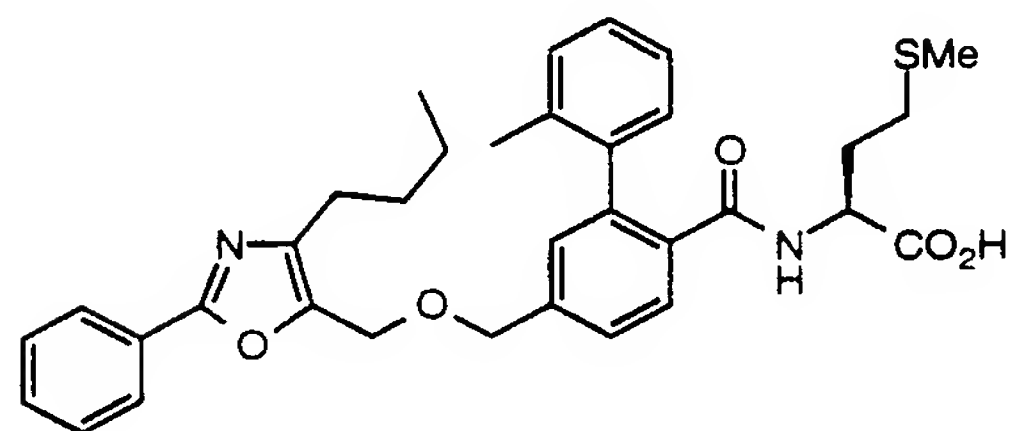
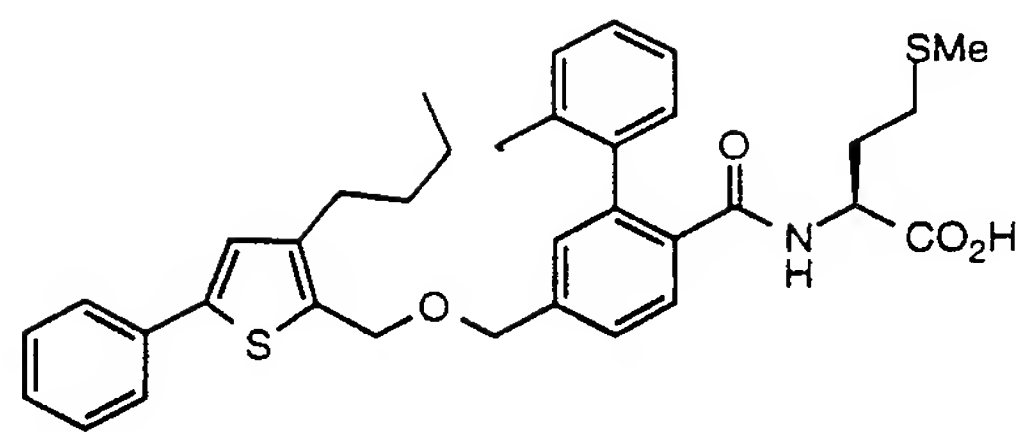
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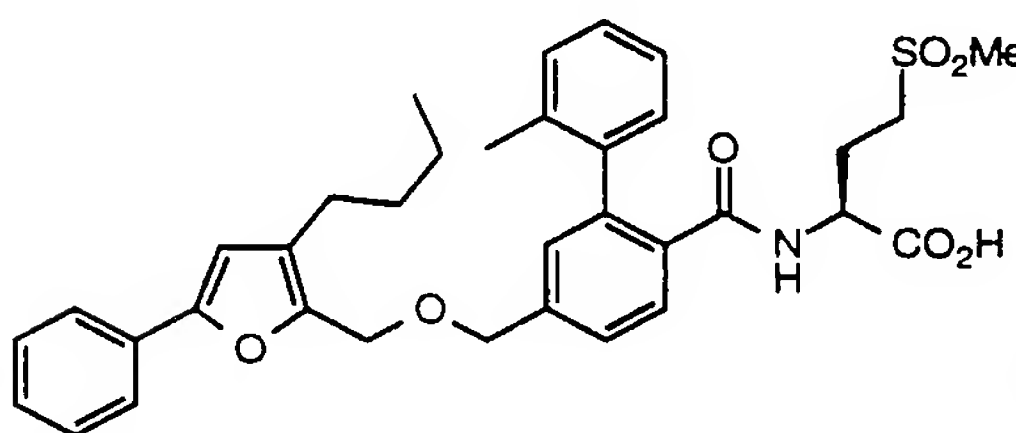
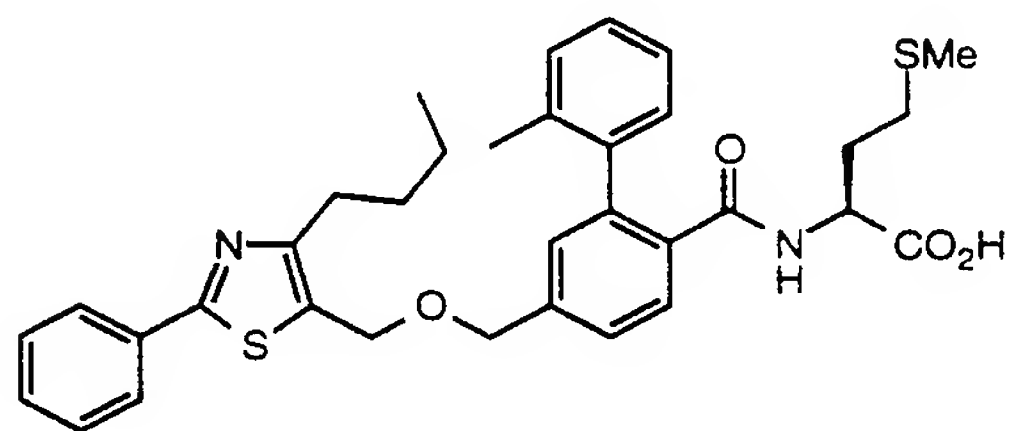




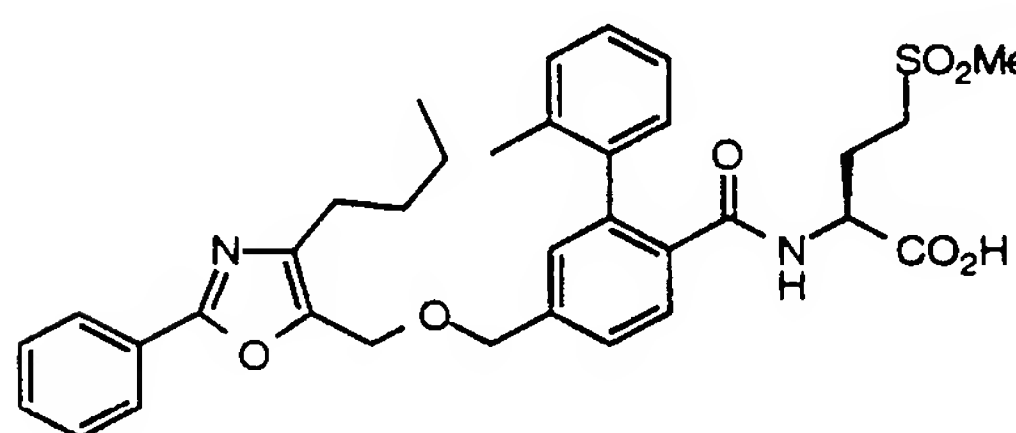
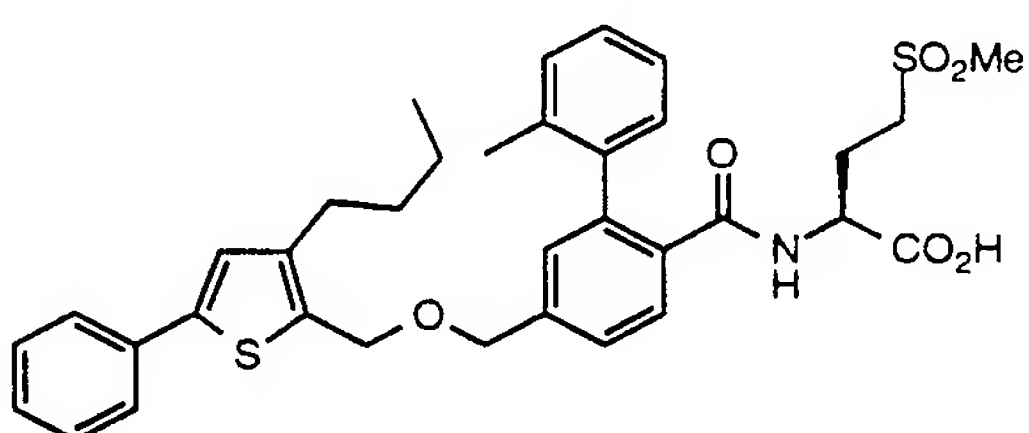
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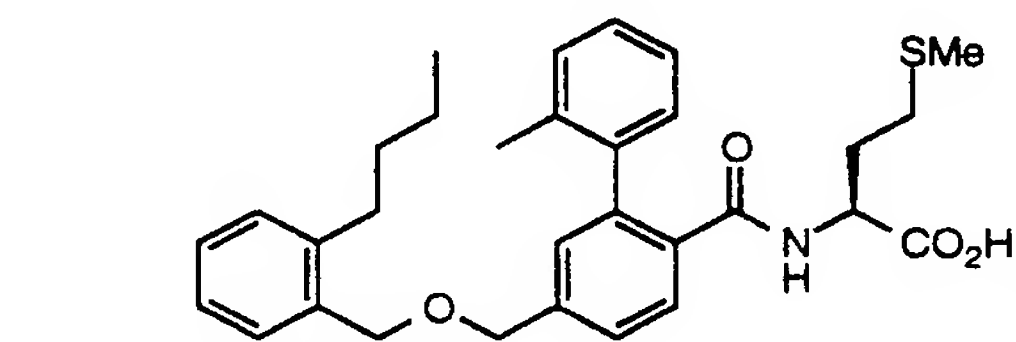
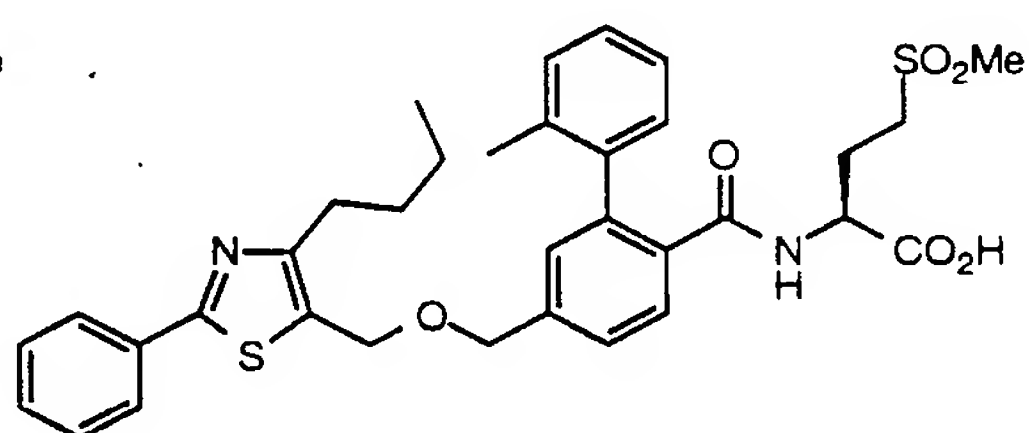
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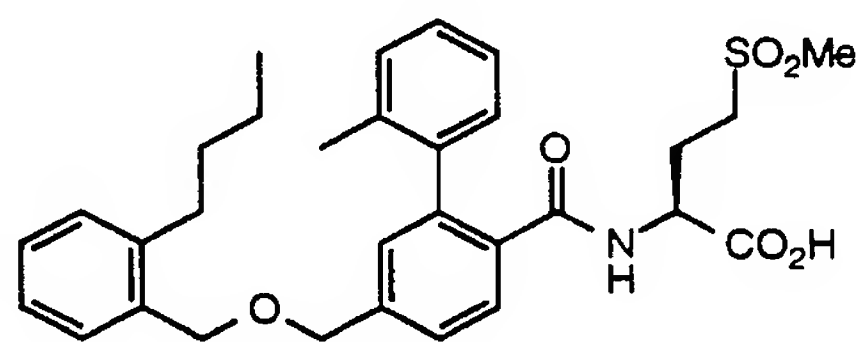
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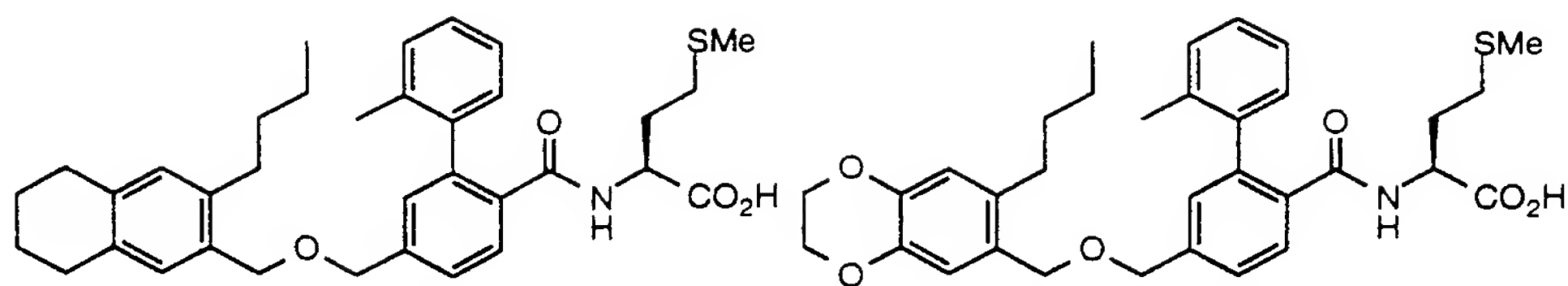


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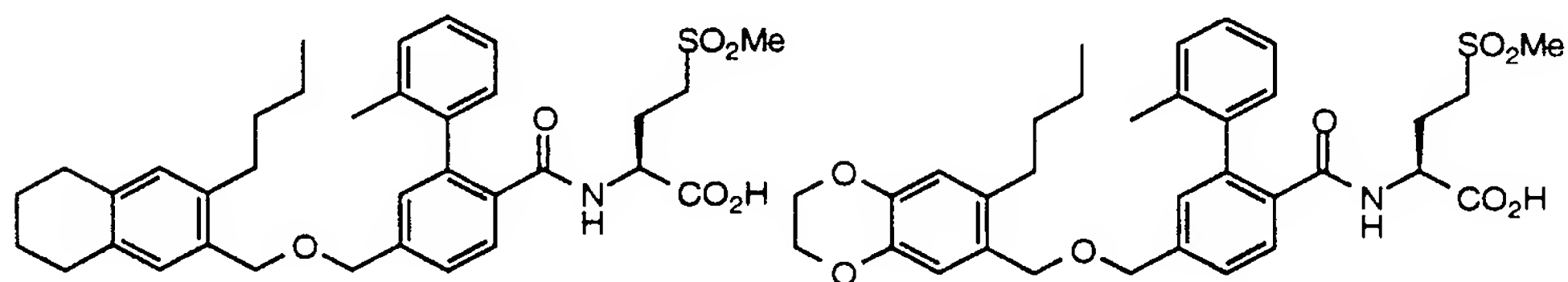


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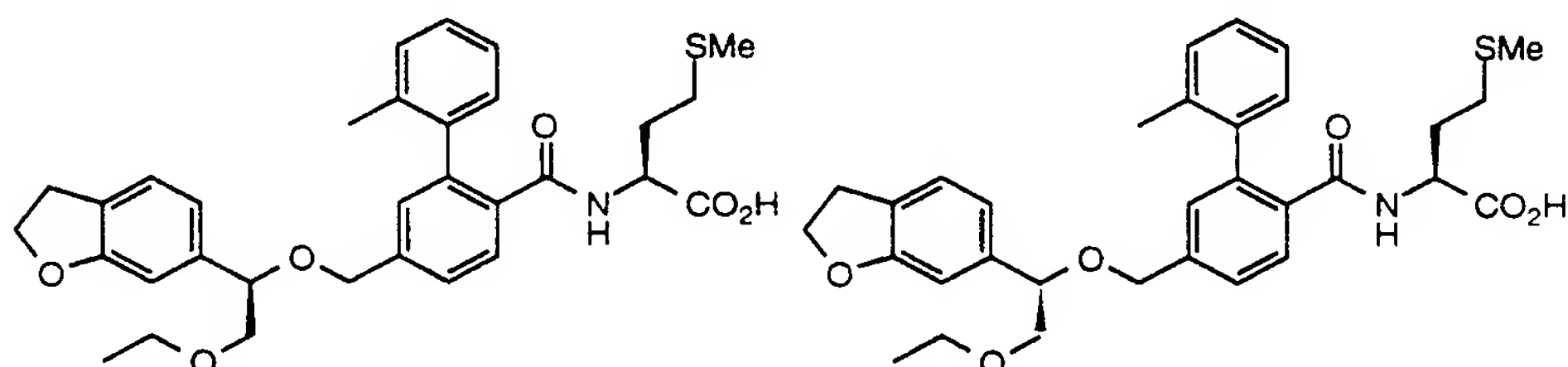




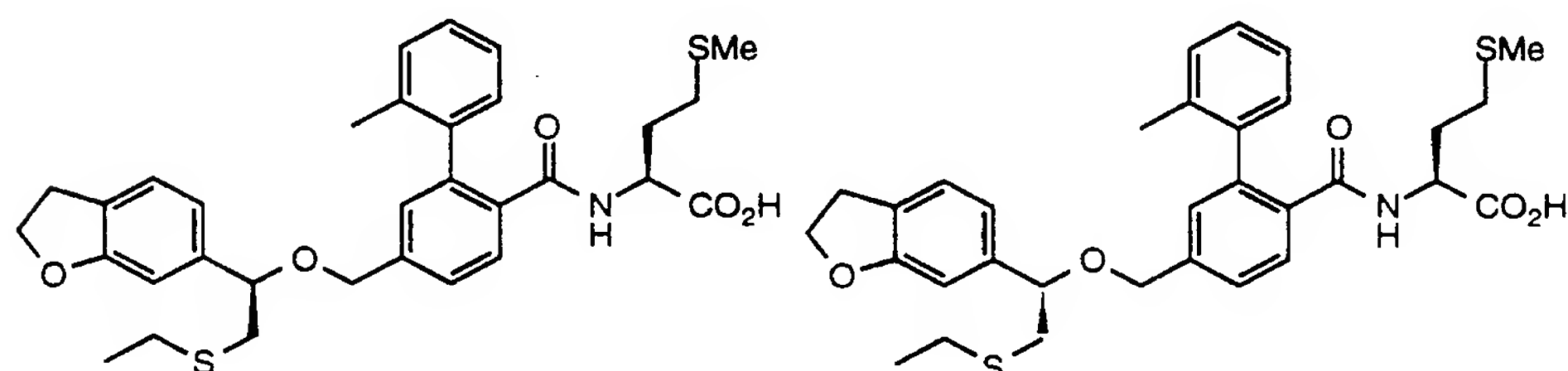
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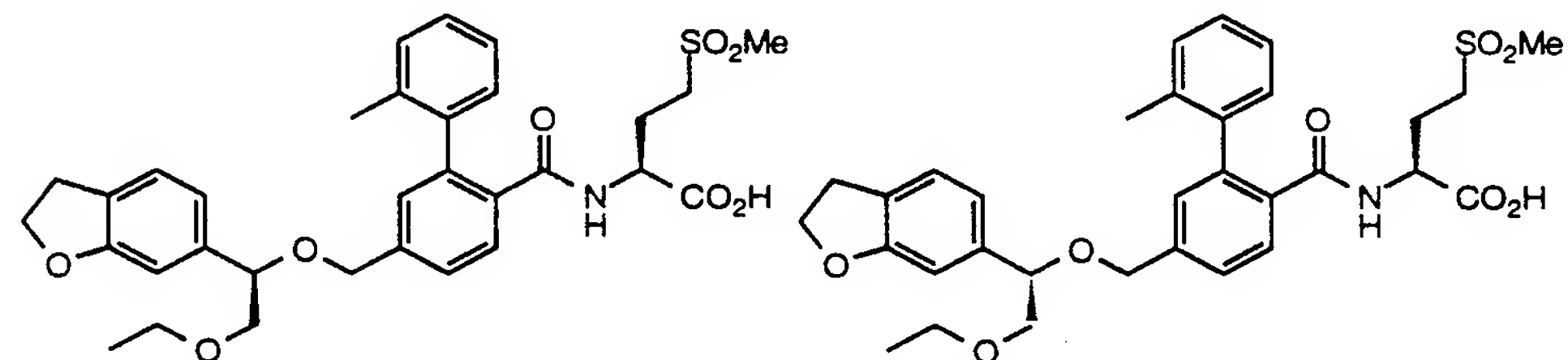
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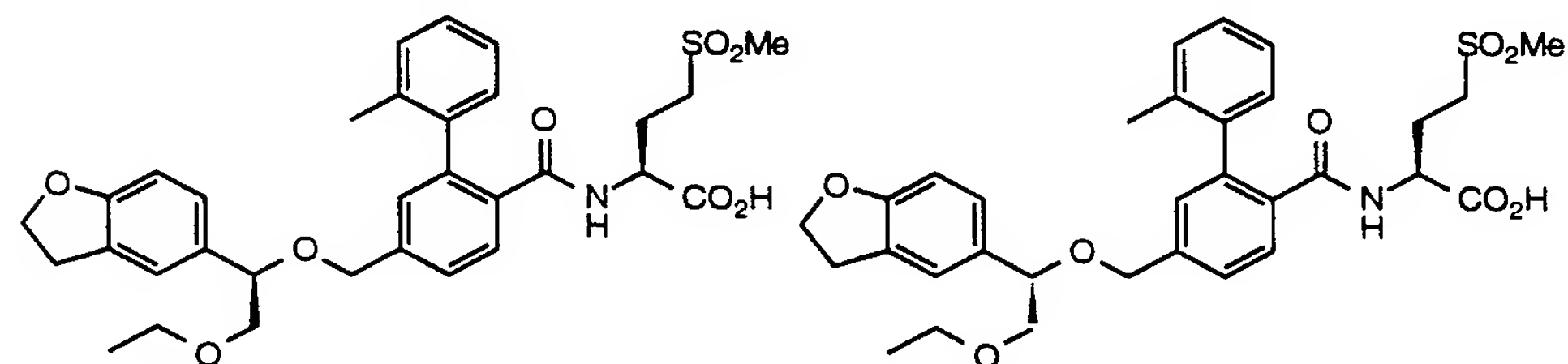
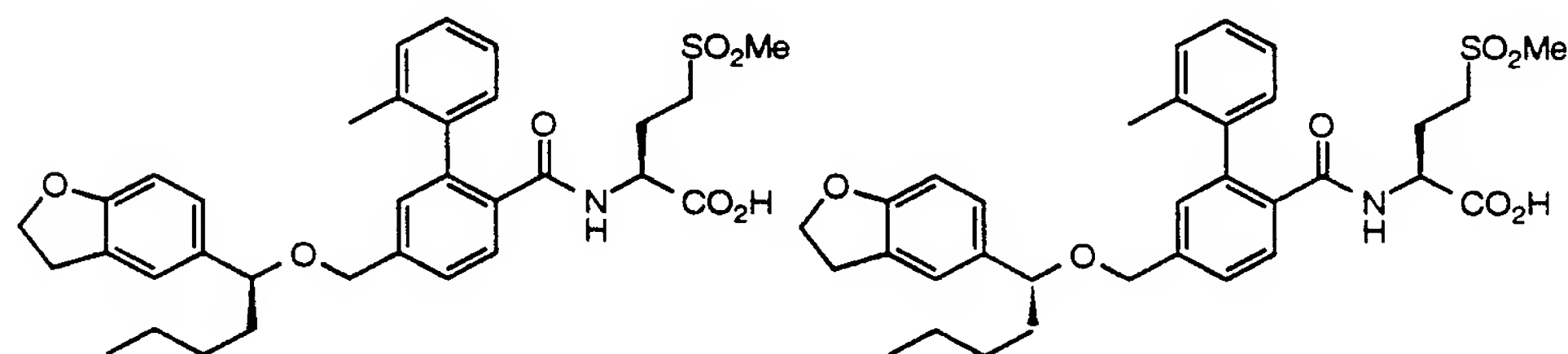
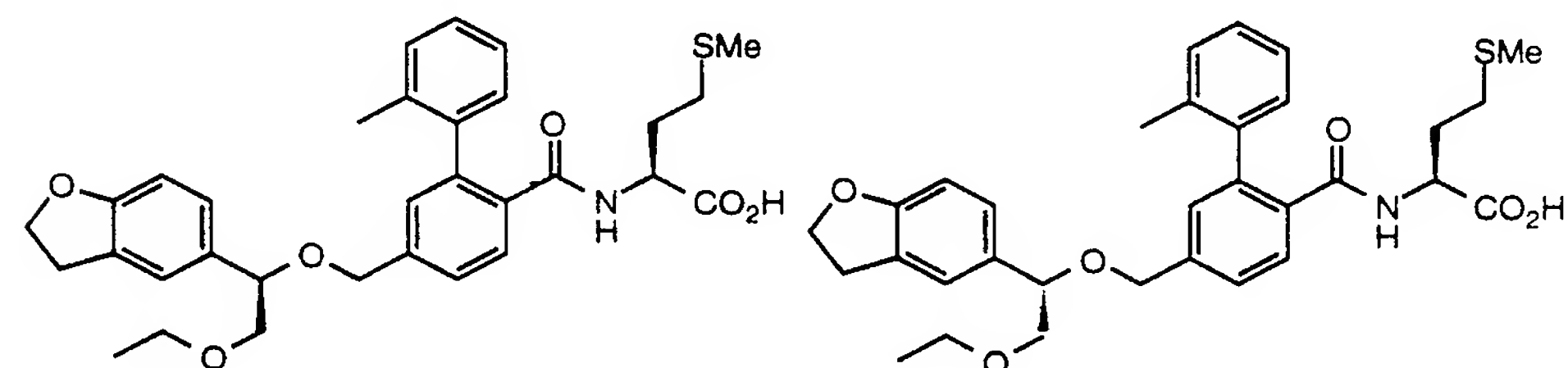
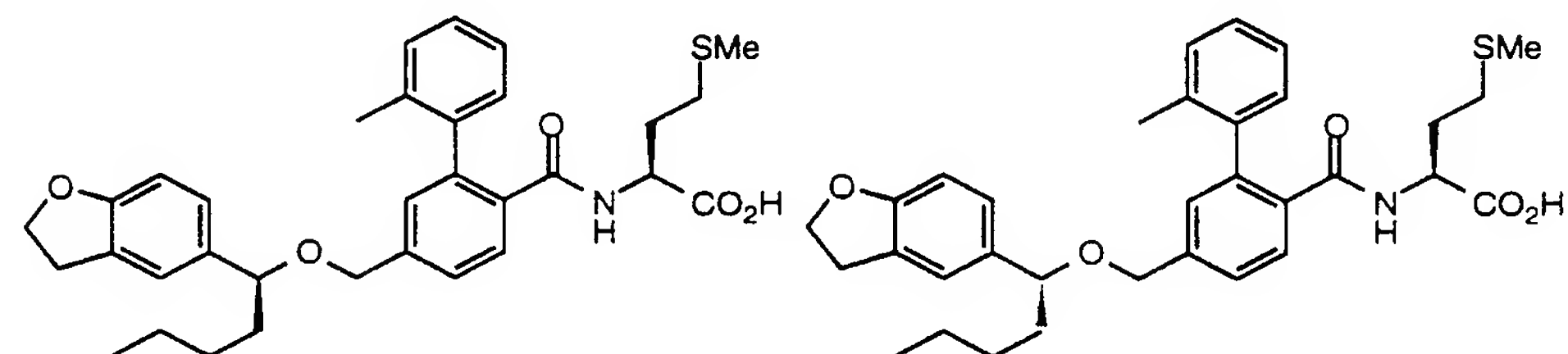
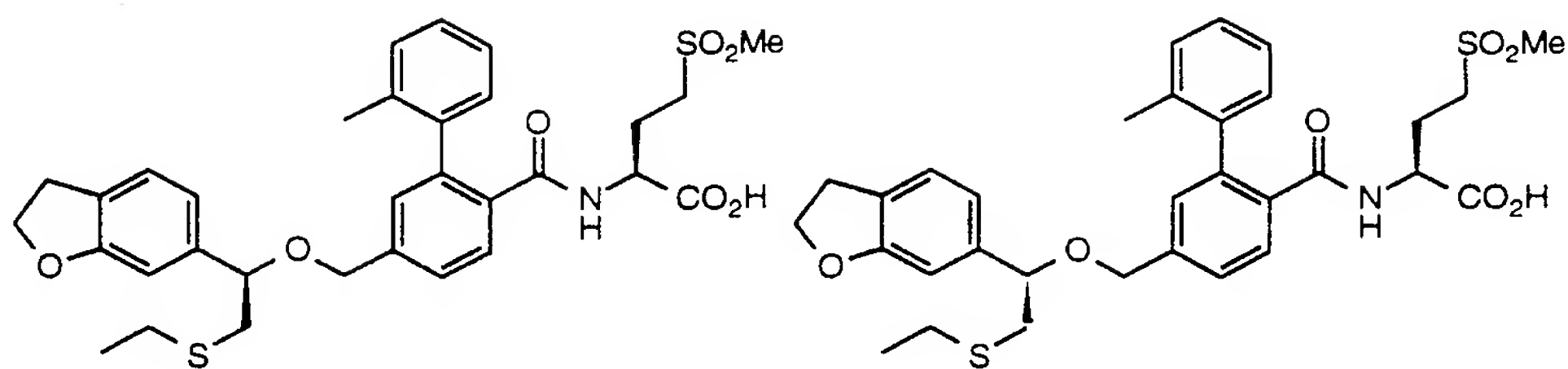
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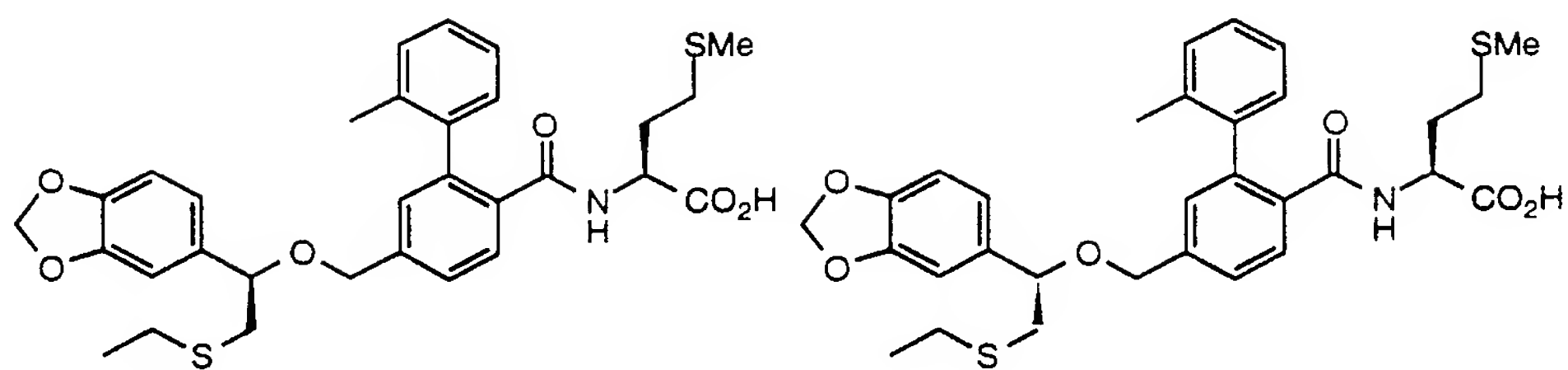
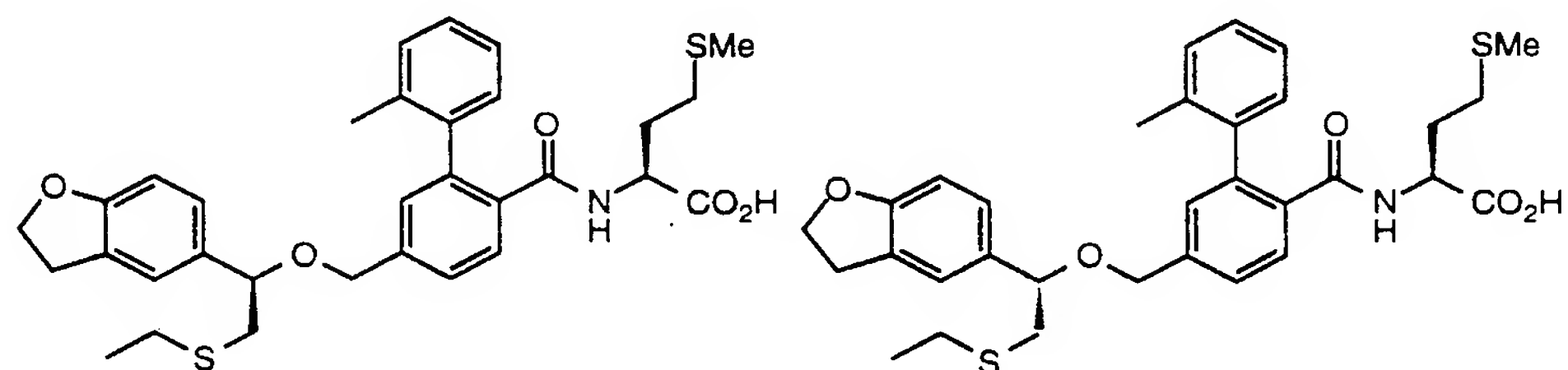
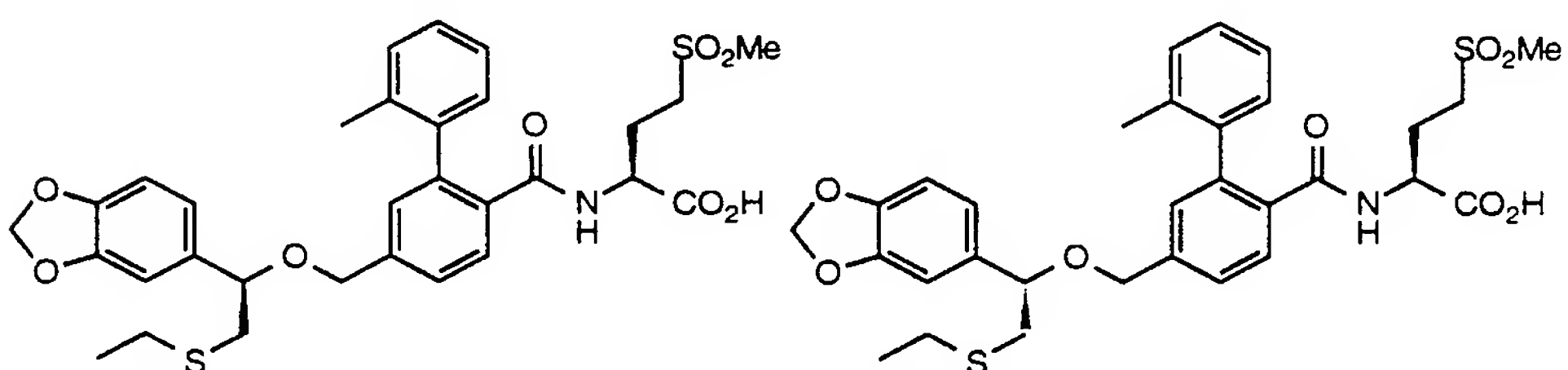
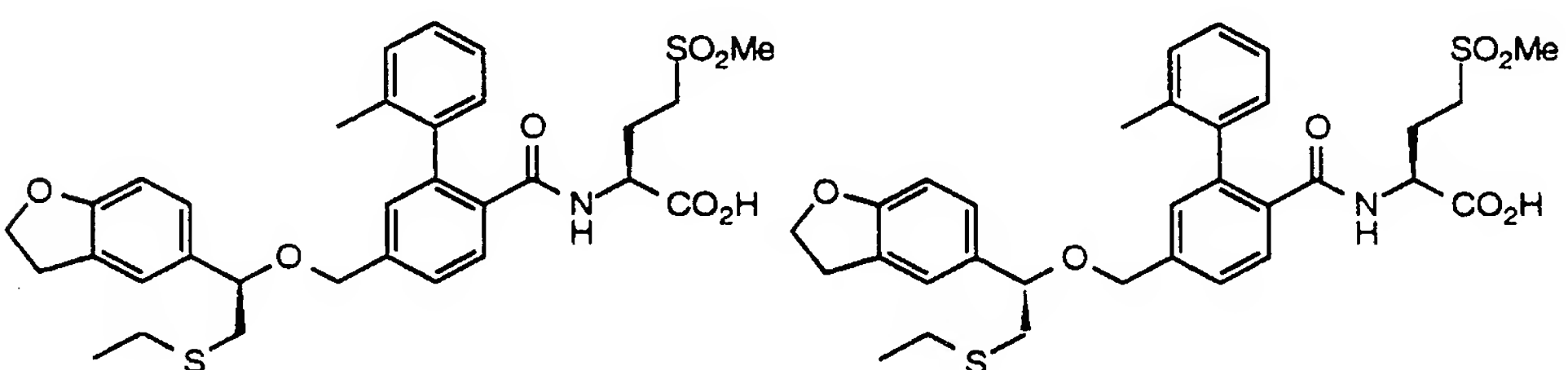
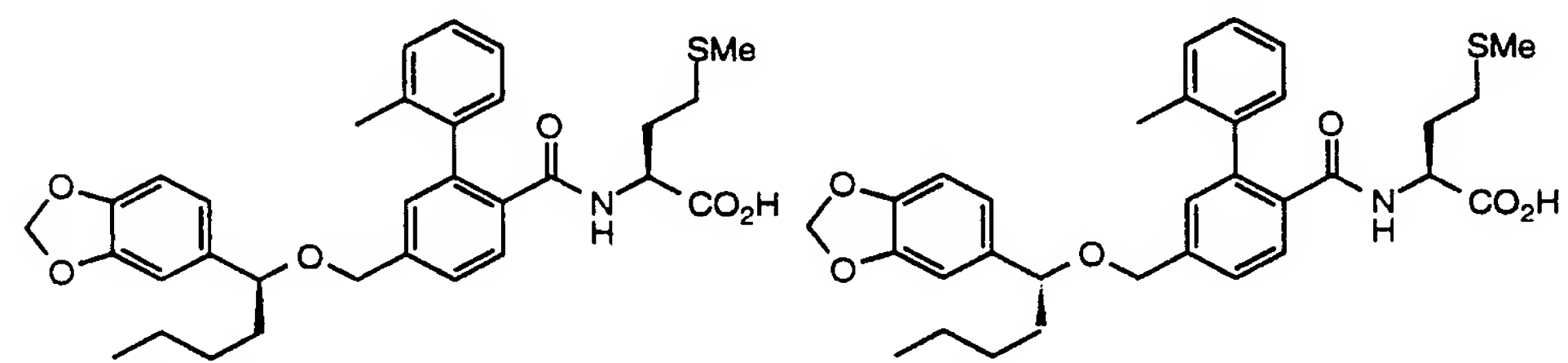


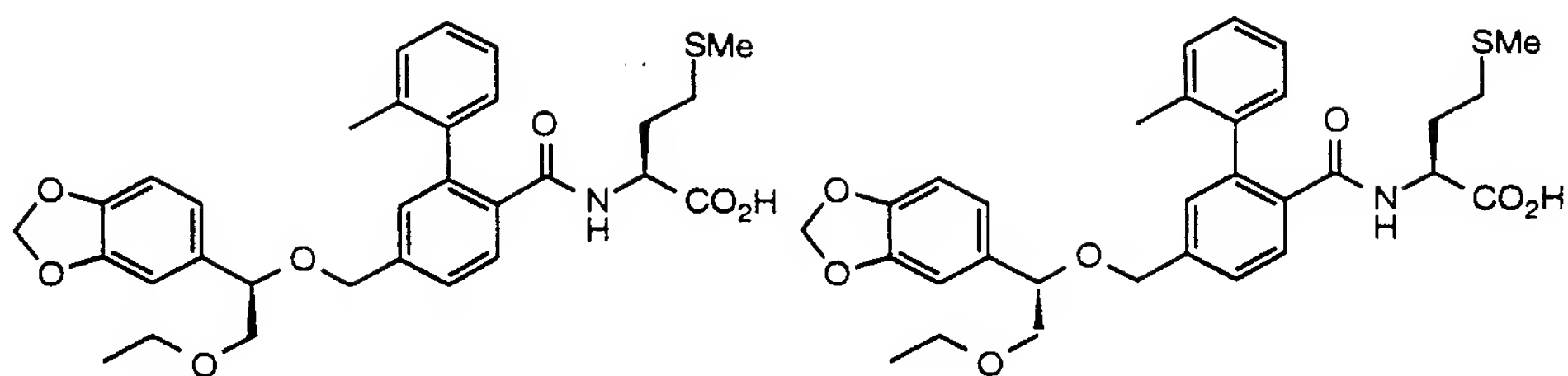
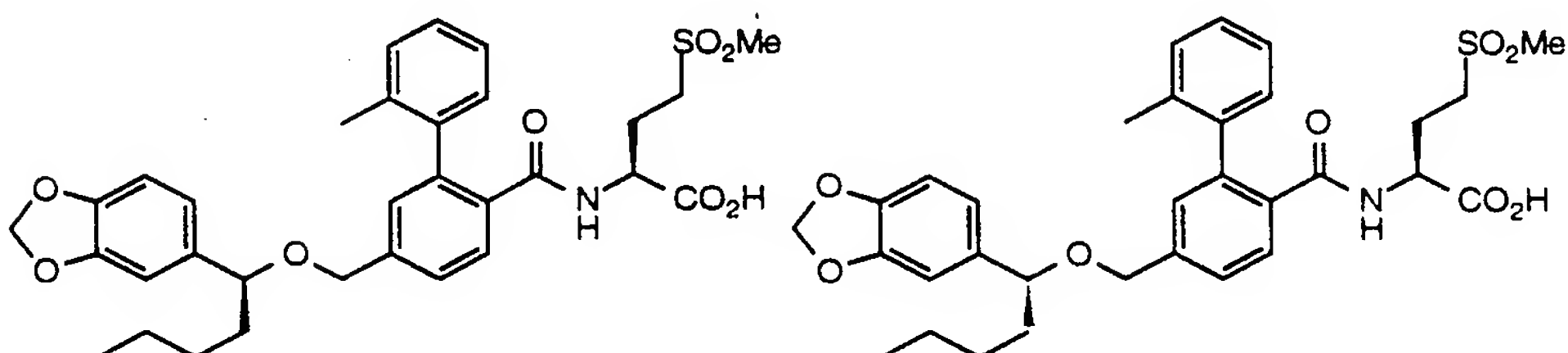
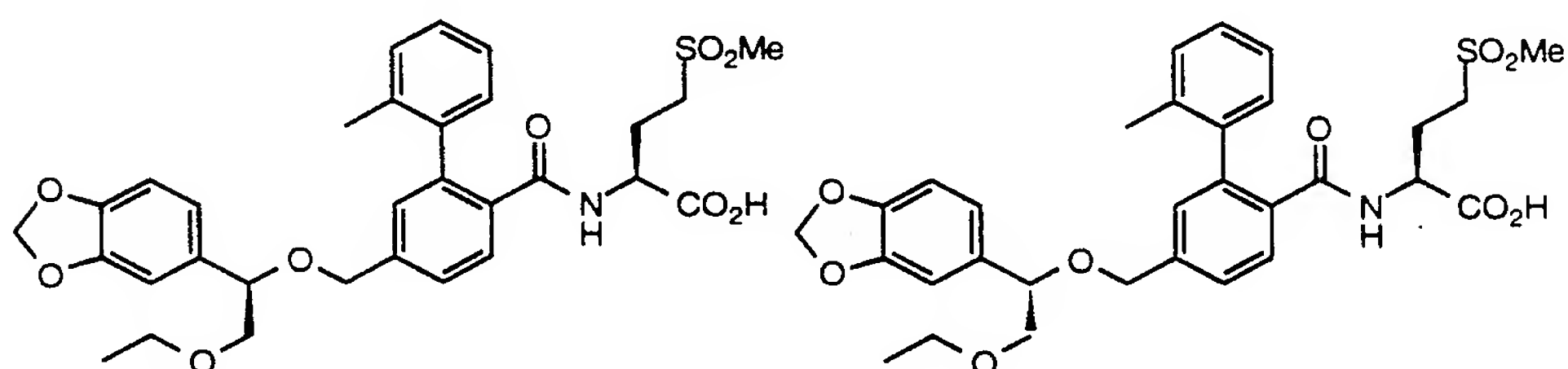
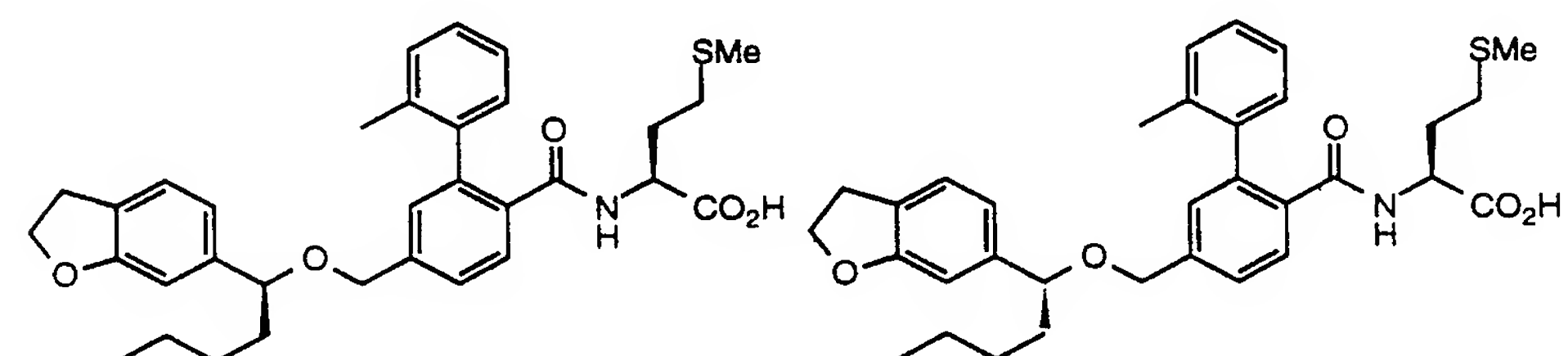
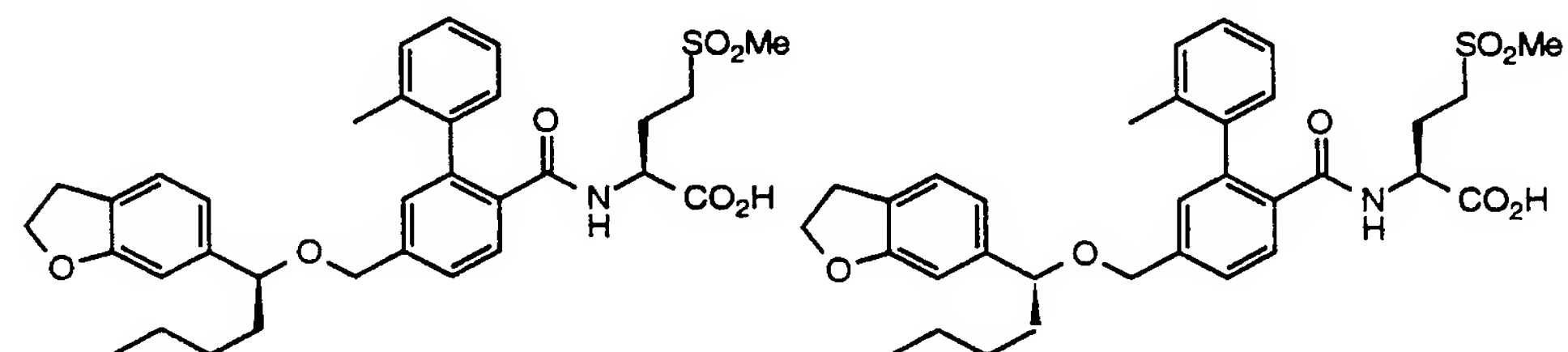
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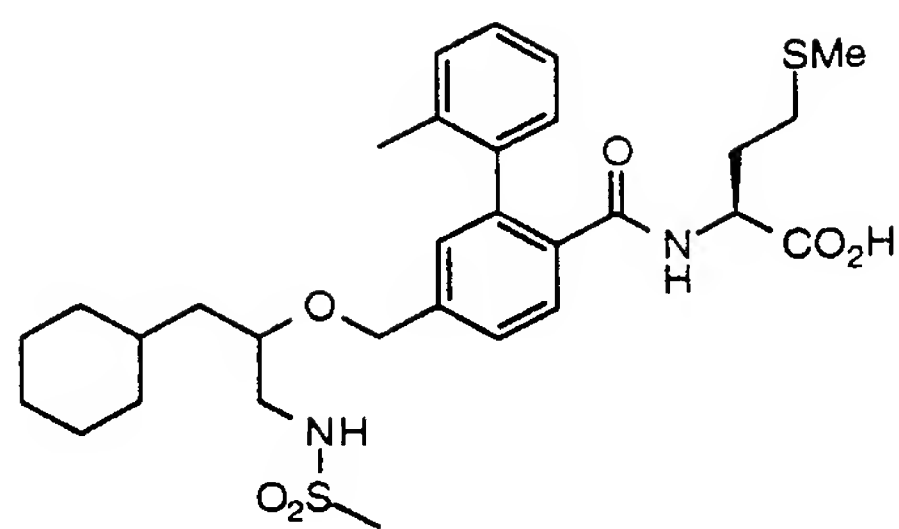


177 178

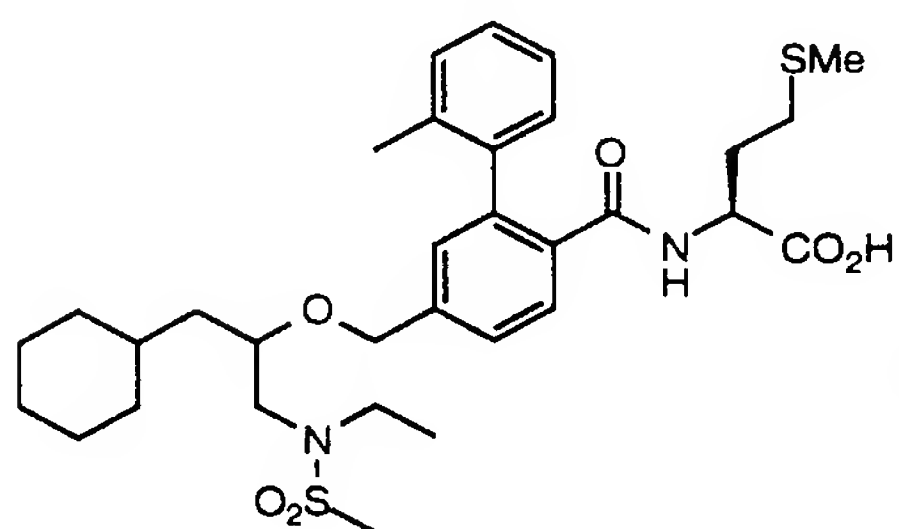
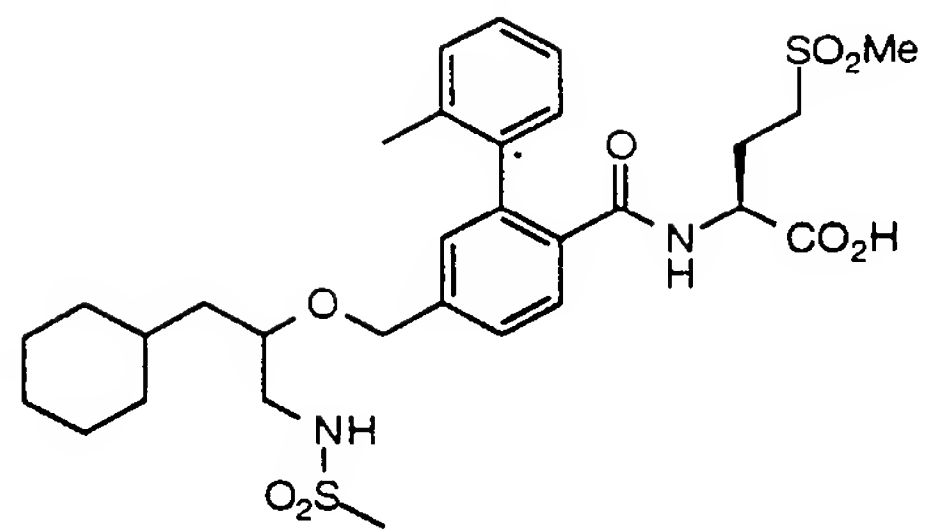


**189 190****191 192****193 194****195 196****197 198**

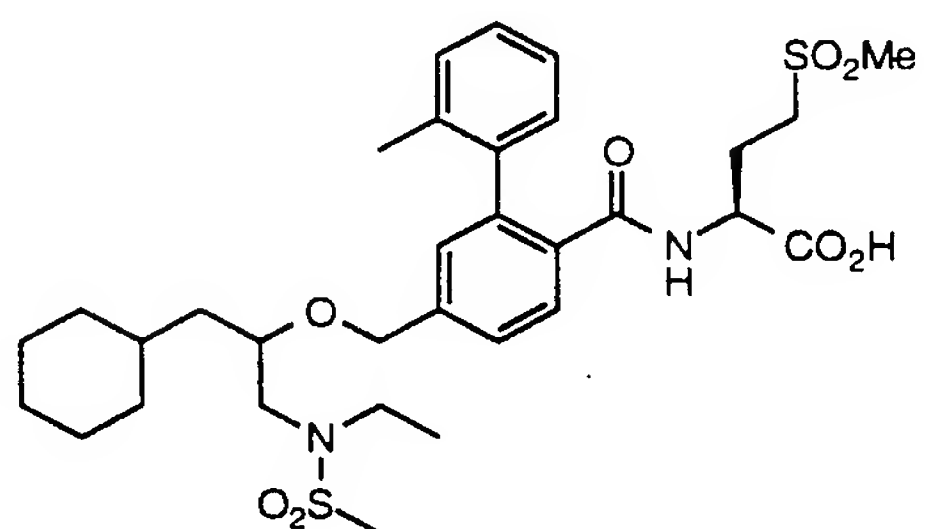
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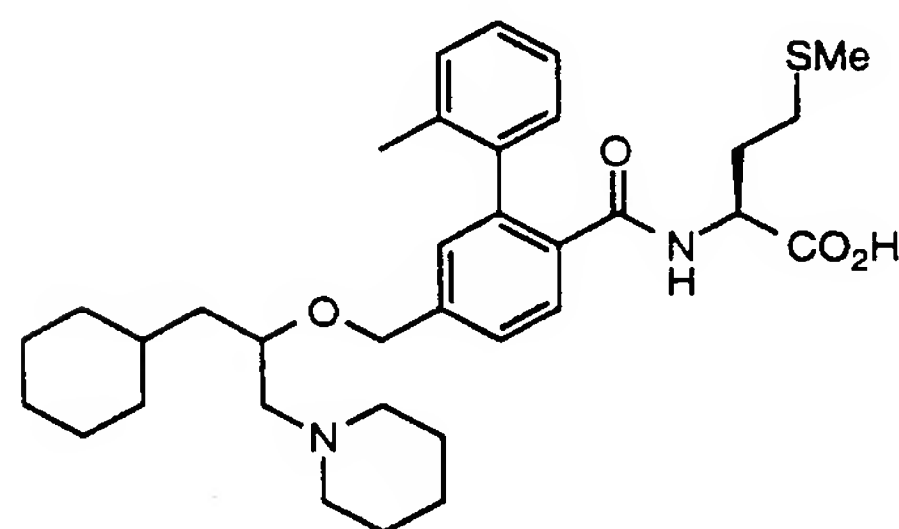
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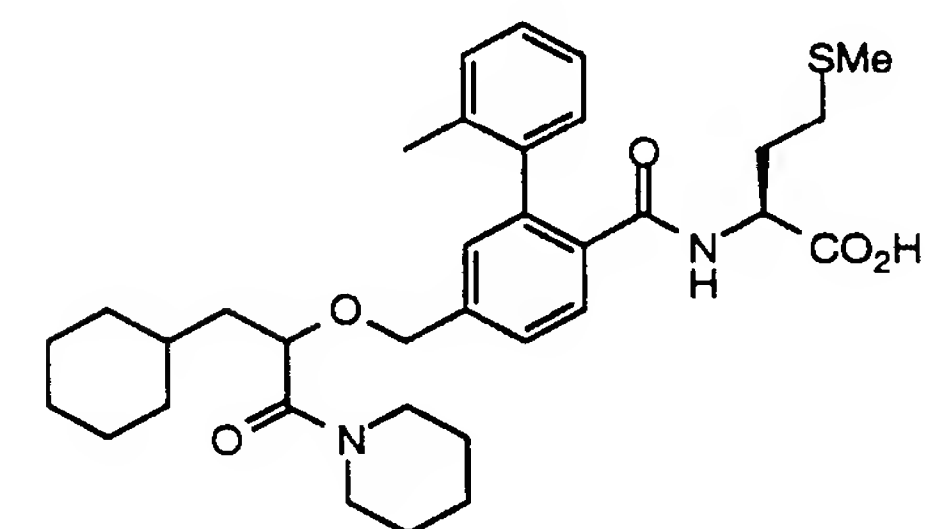
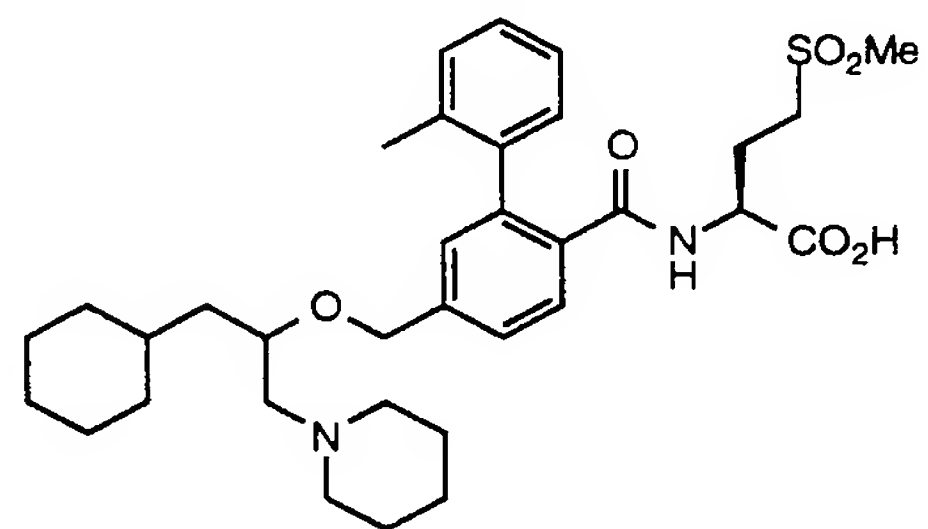
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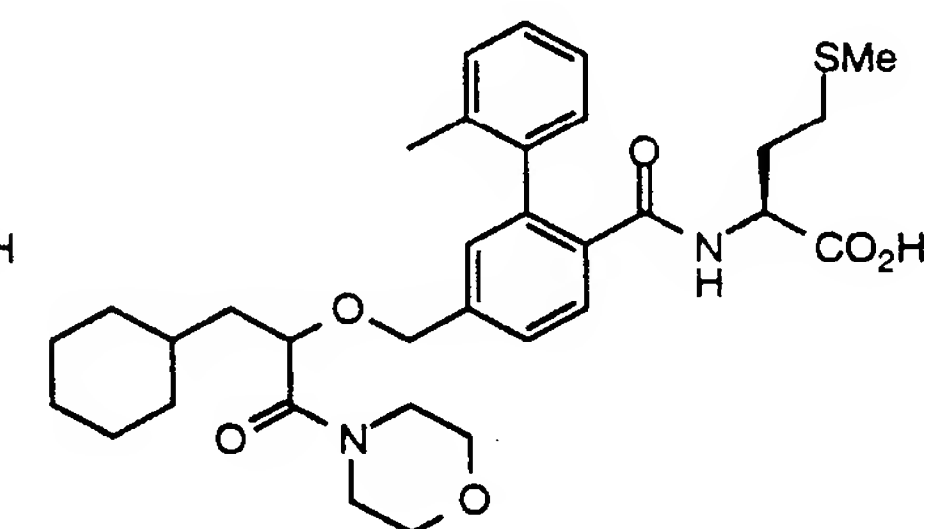
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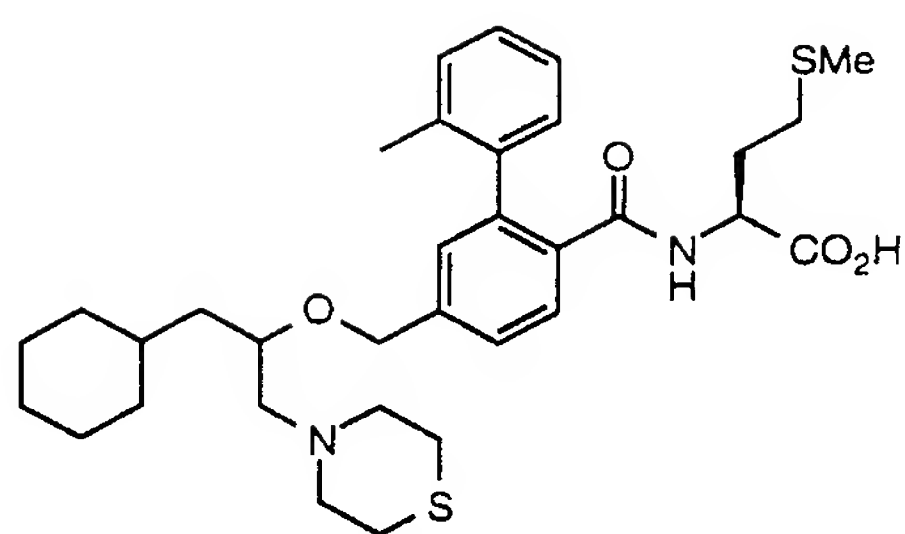
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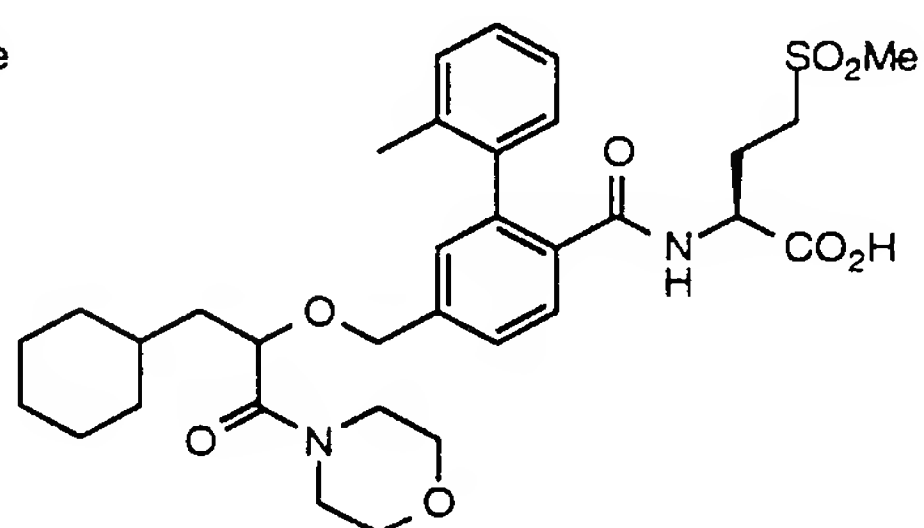
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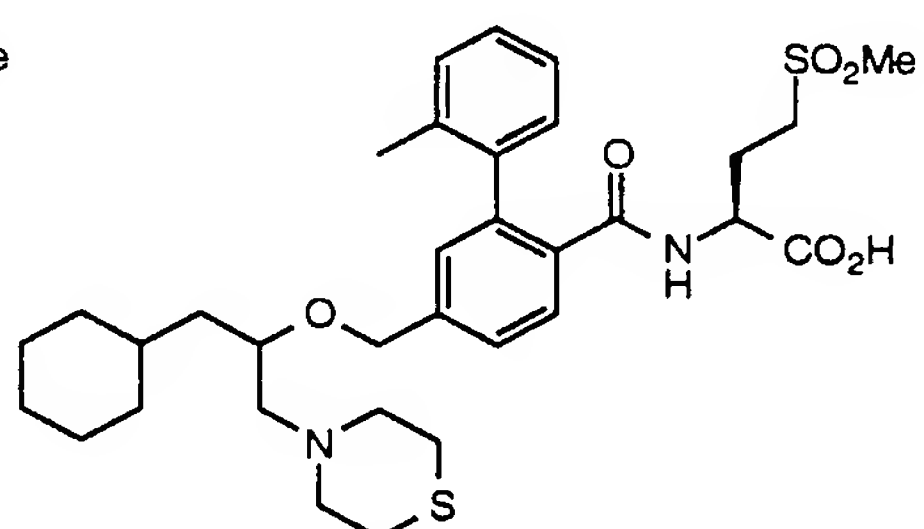
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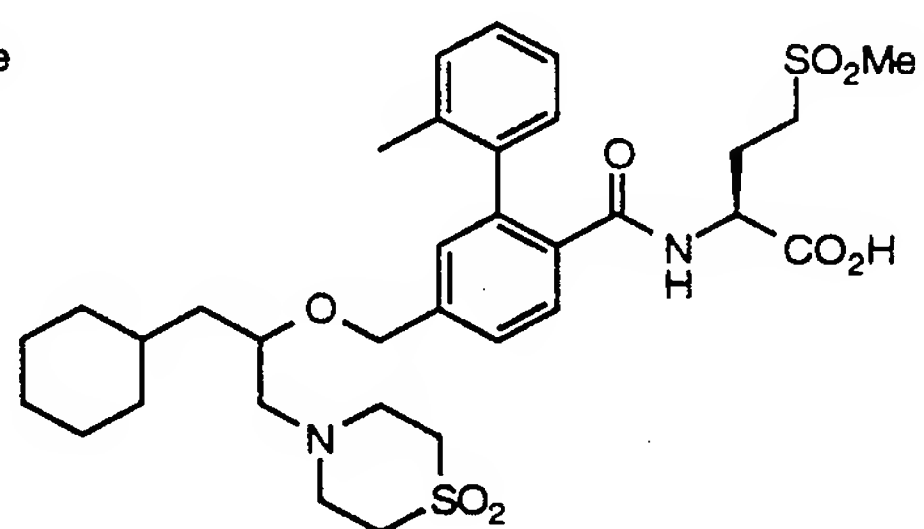
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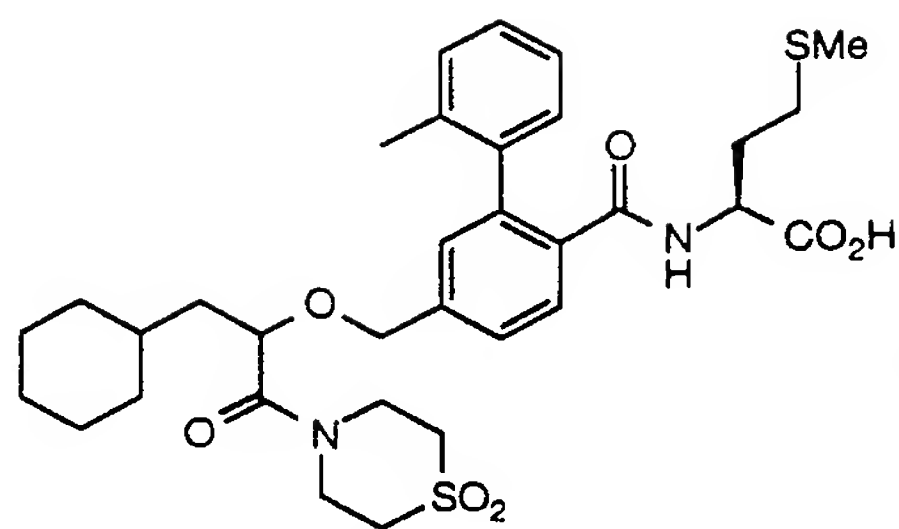
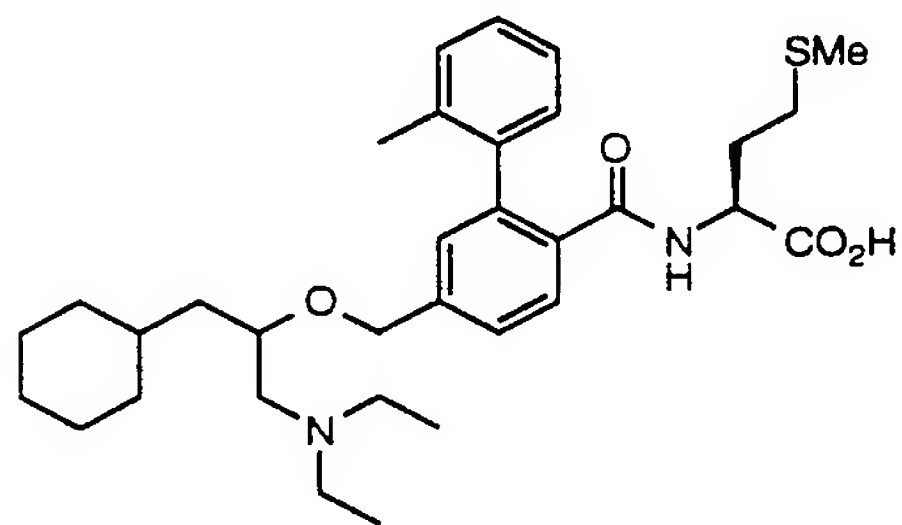
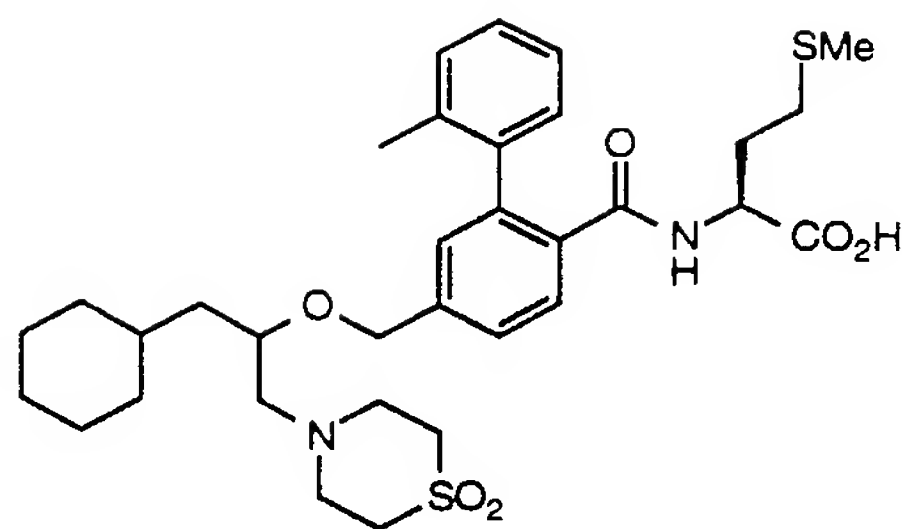
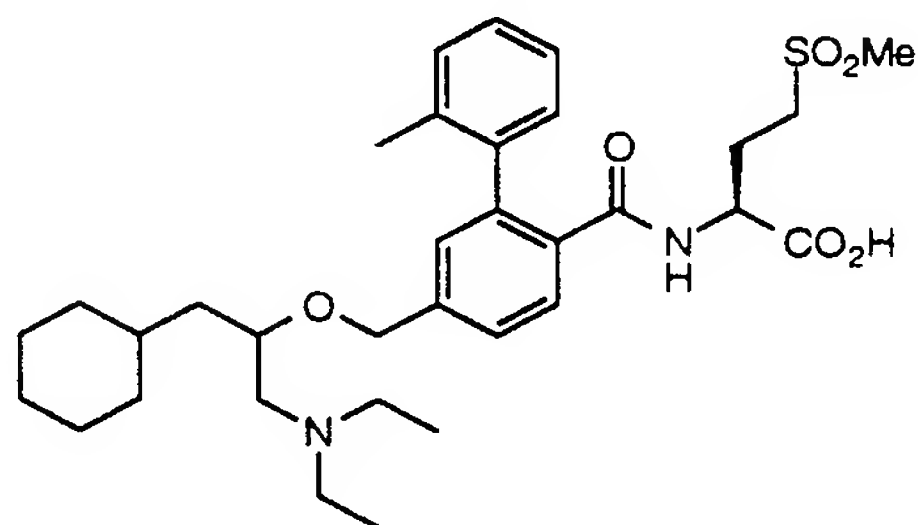
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**223      224**

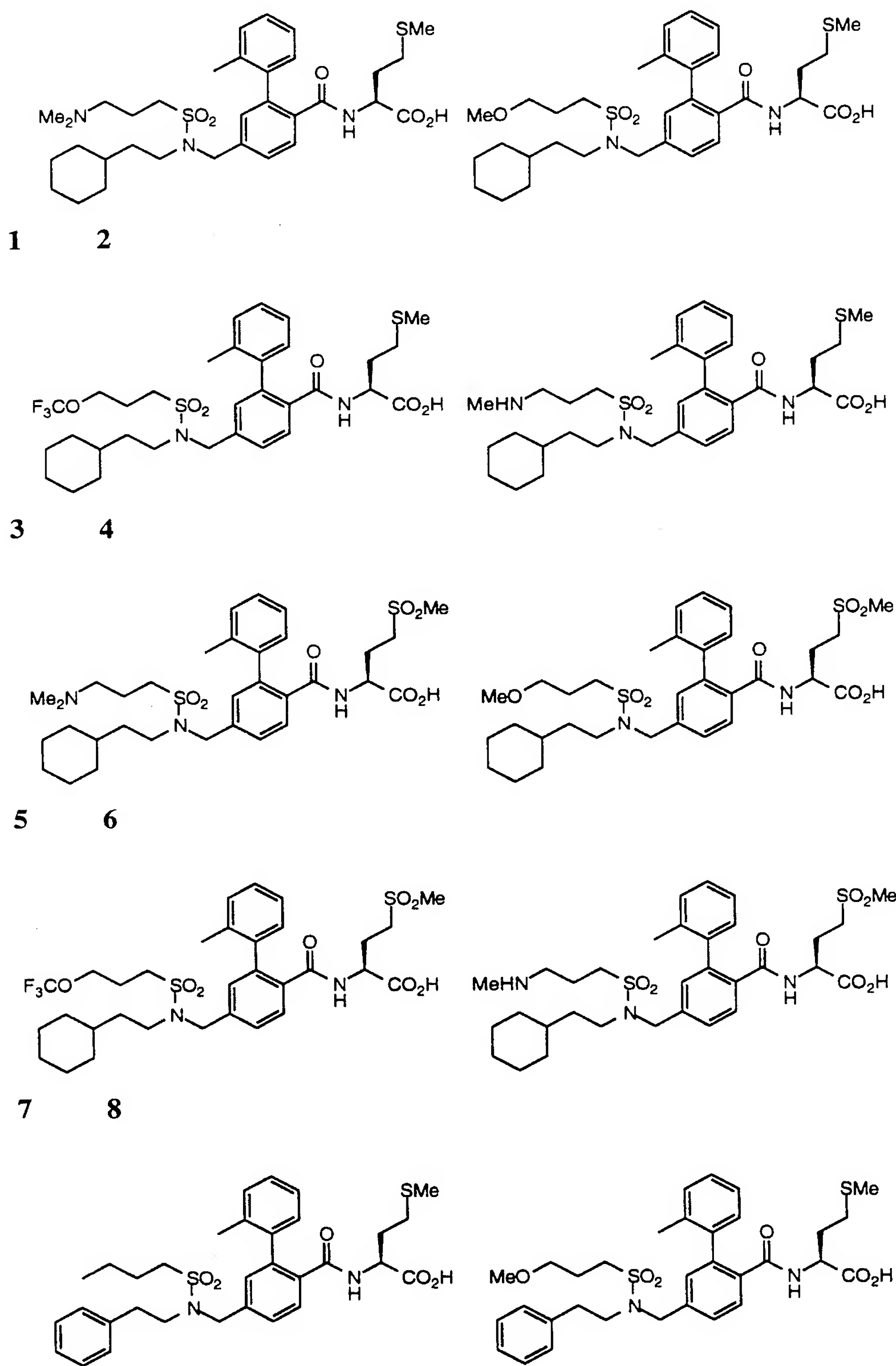


2435

**225 226****227 228**

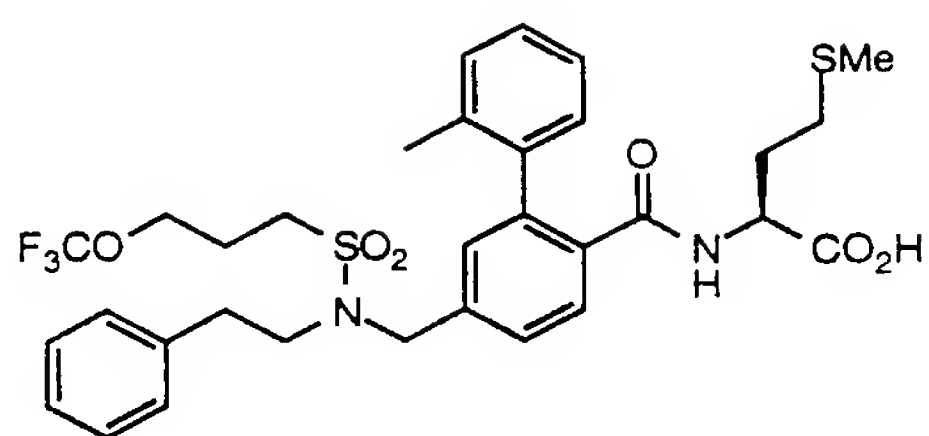


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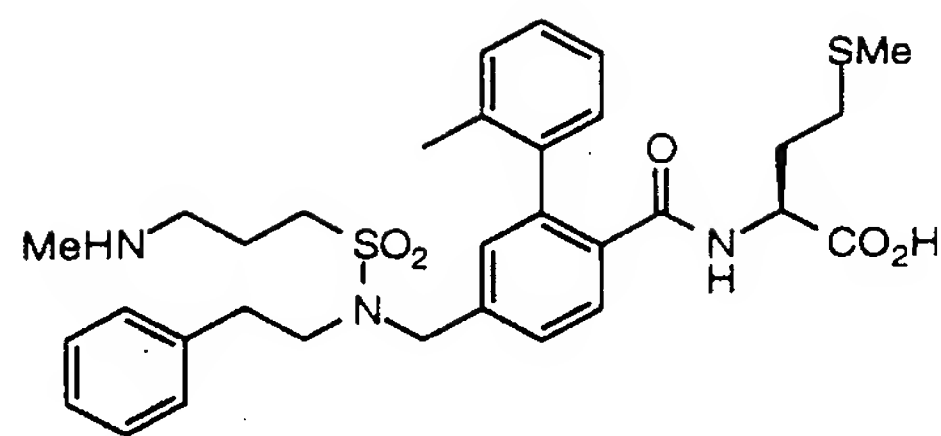
Table 8. Sulfonamides of the Type  $ASO_2(B)N-L_1$ 

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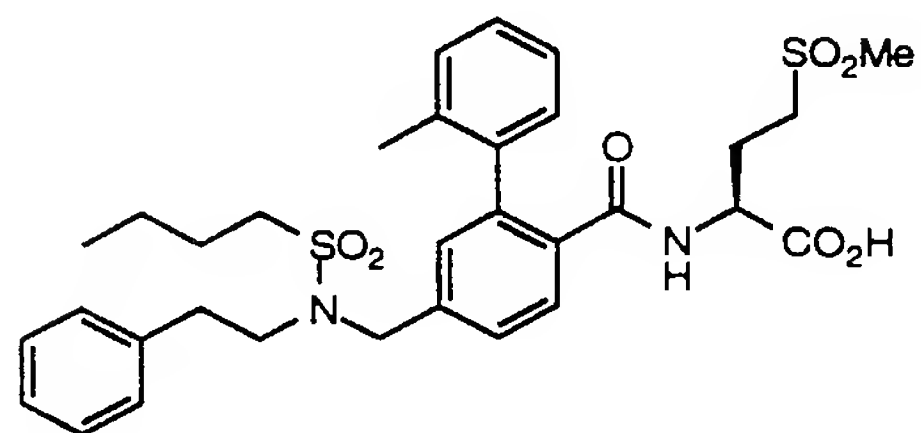
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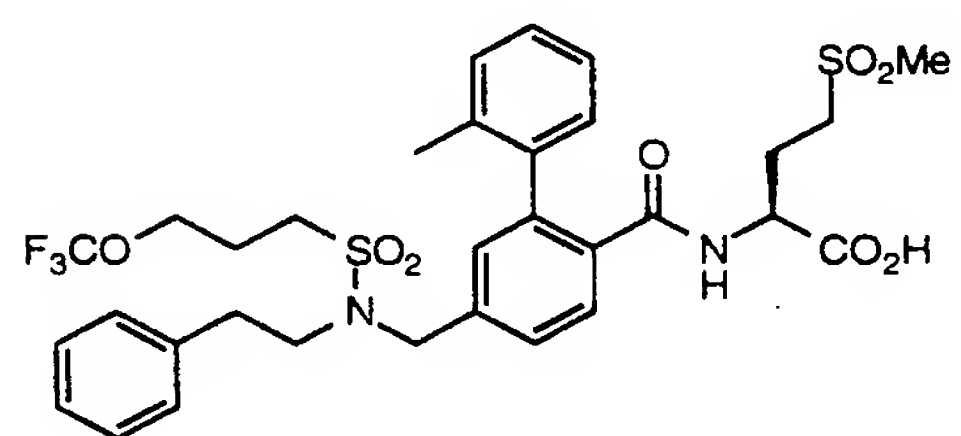
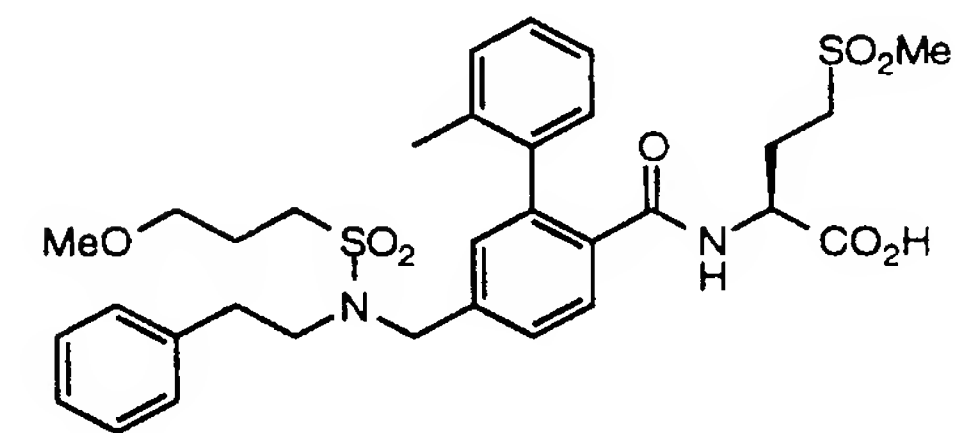
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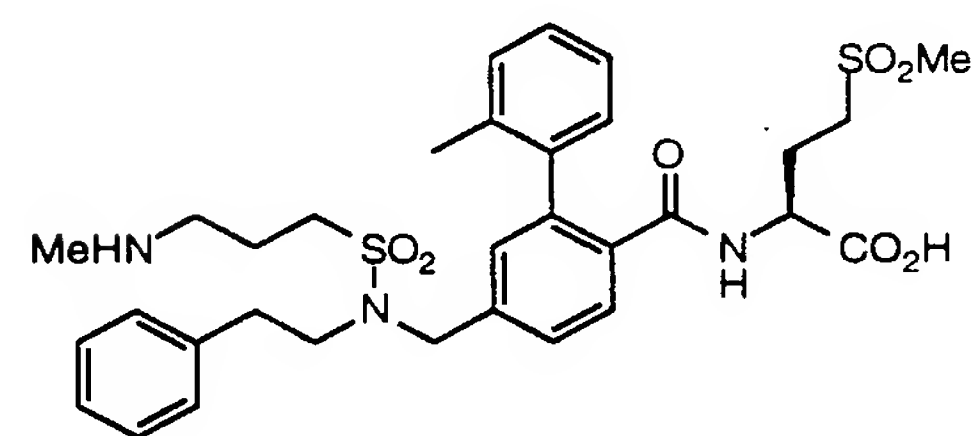
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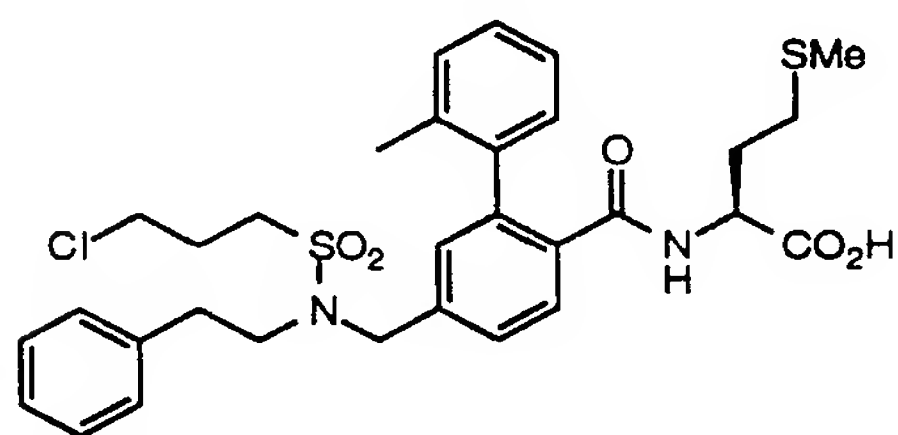
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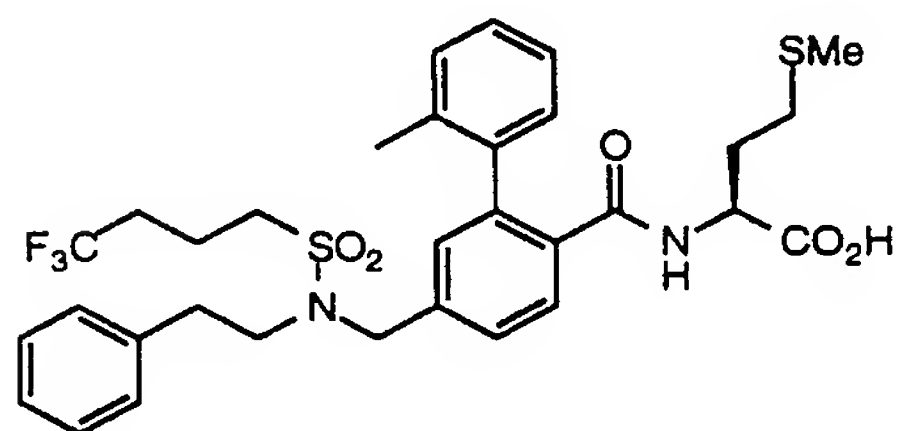
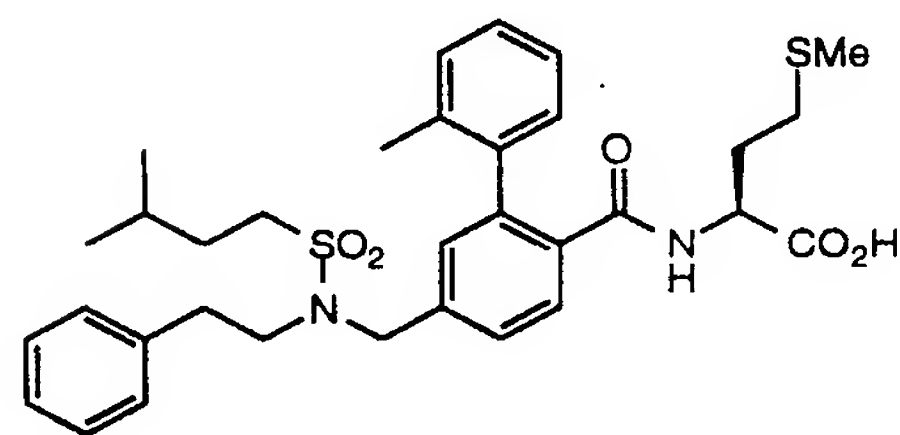
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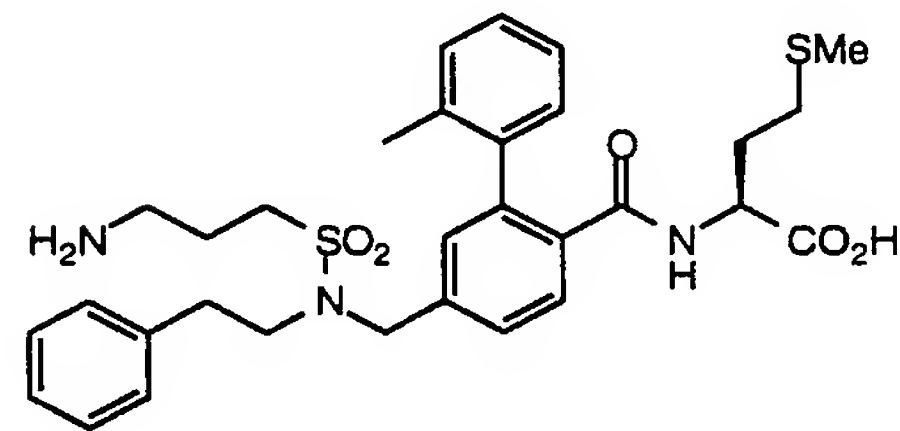
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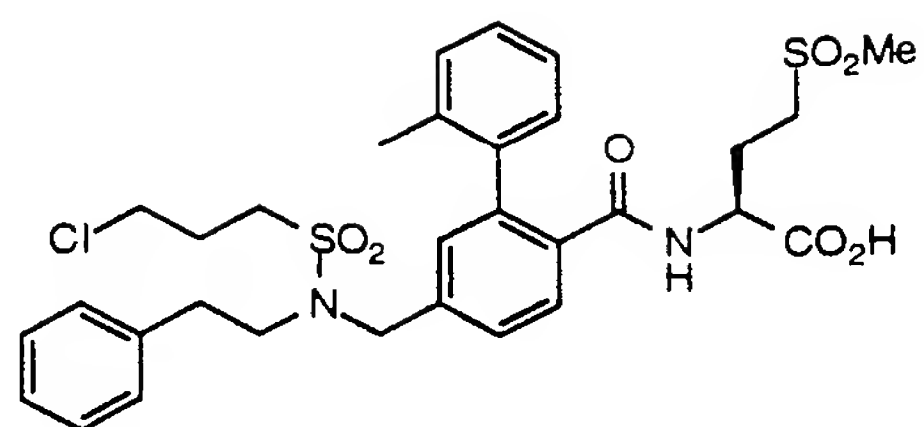
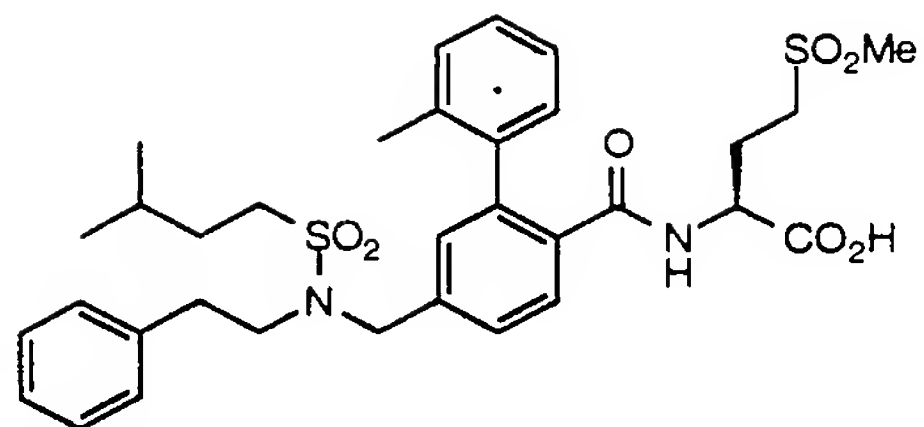
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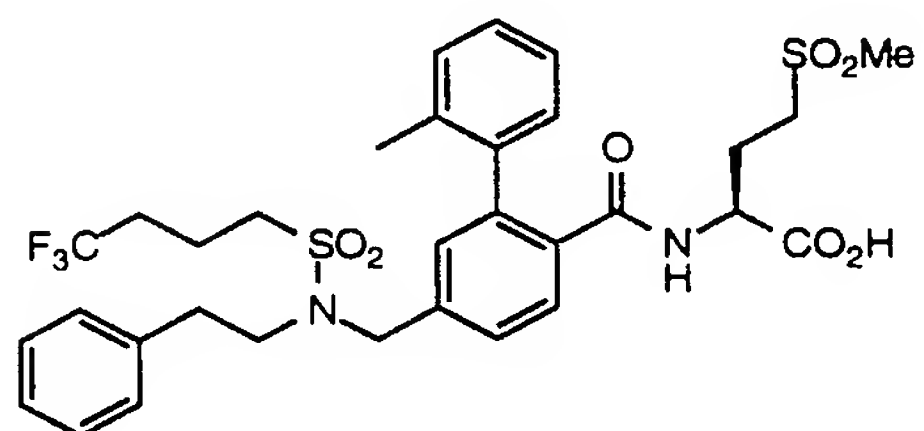
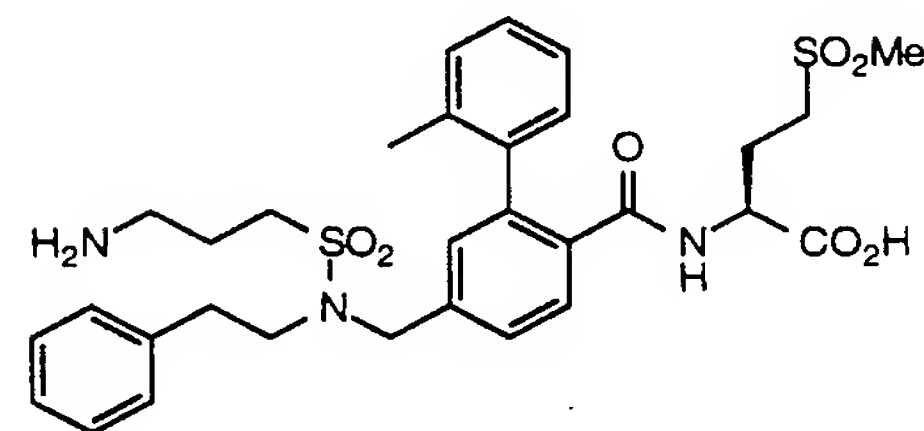
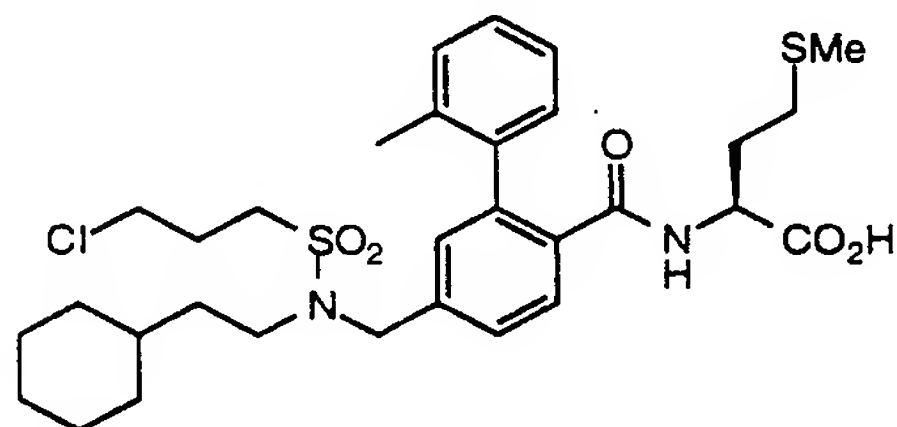
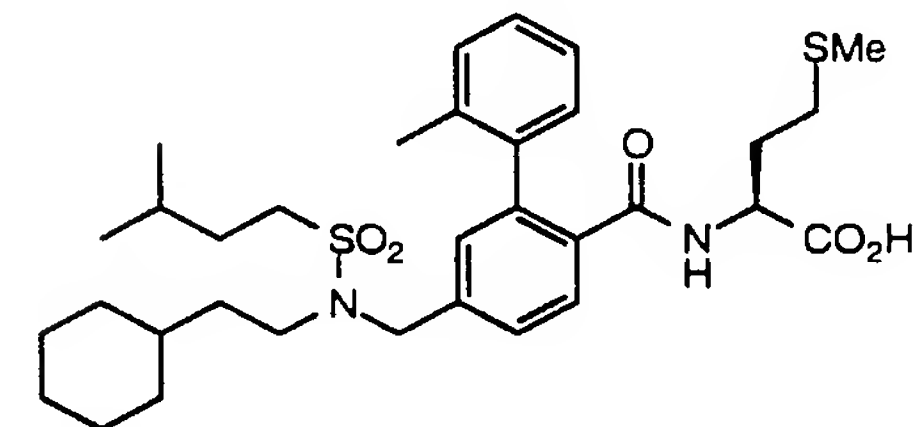
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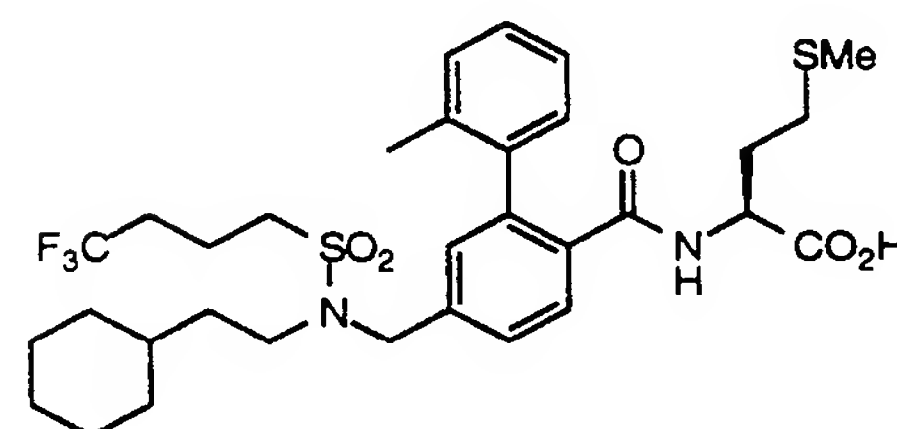
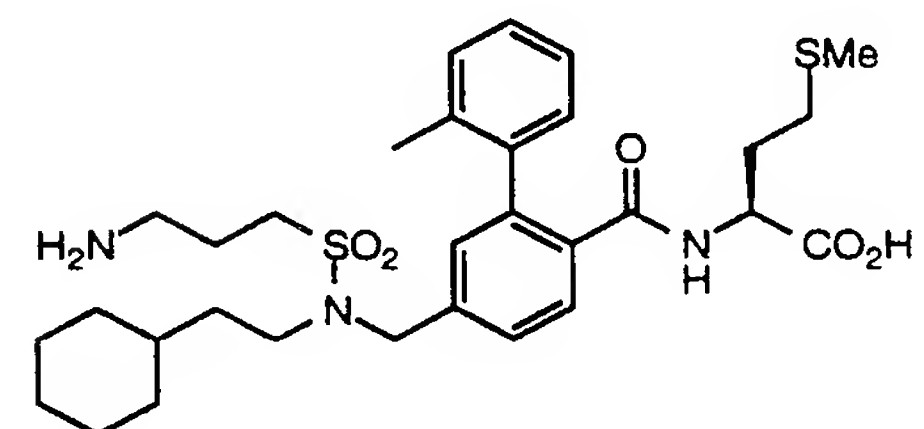
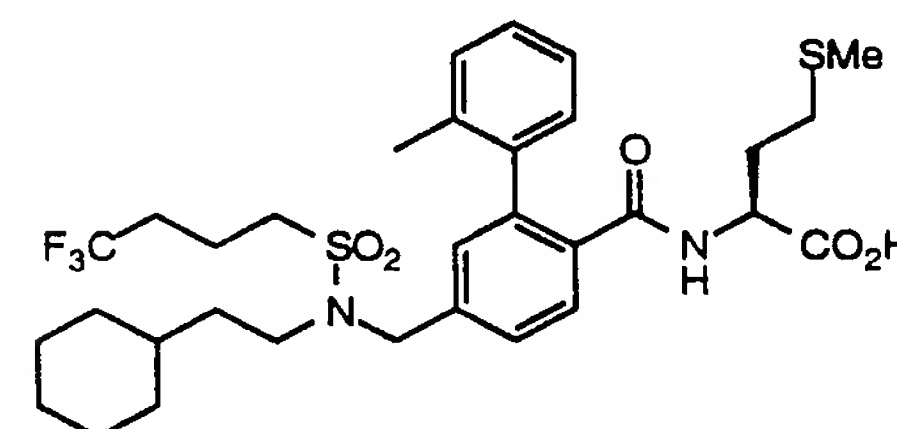
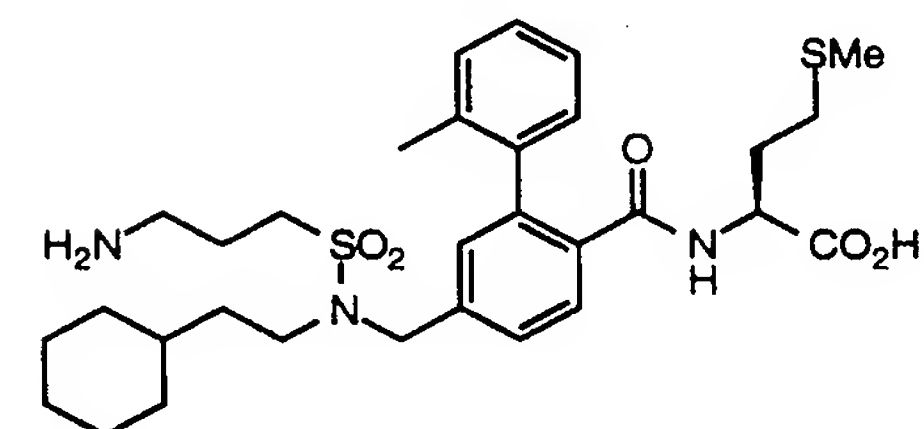
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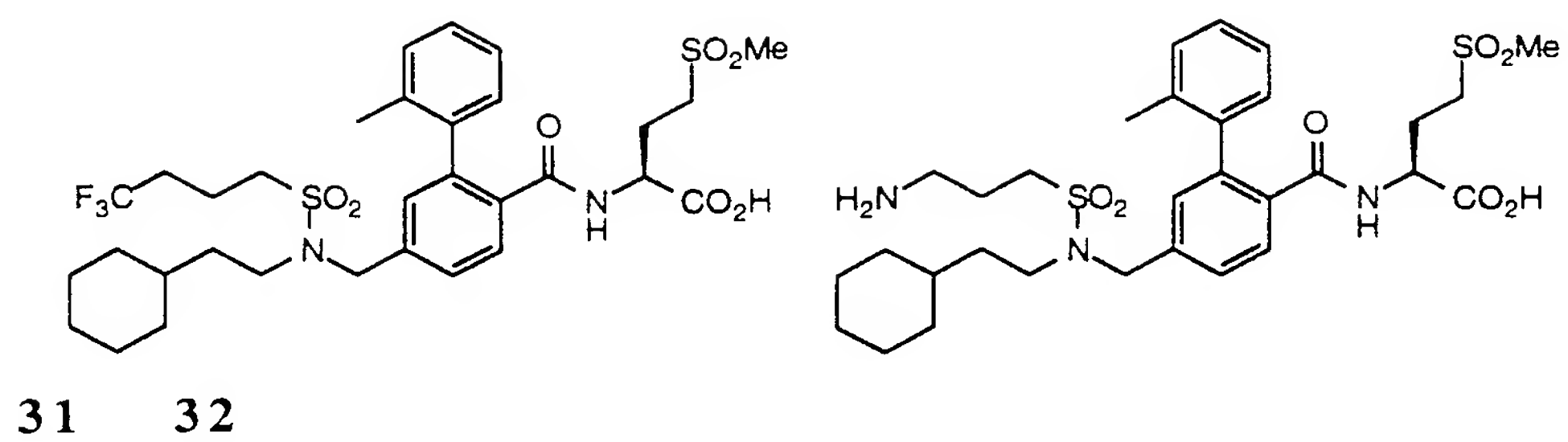
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**23****24****25****26**

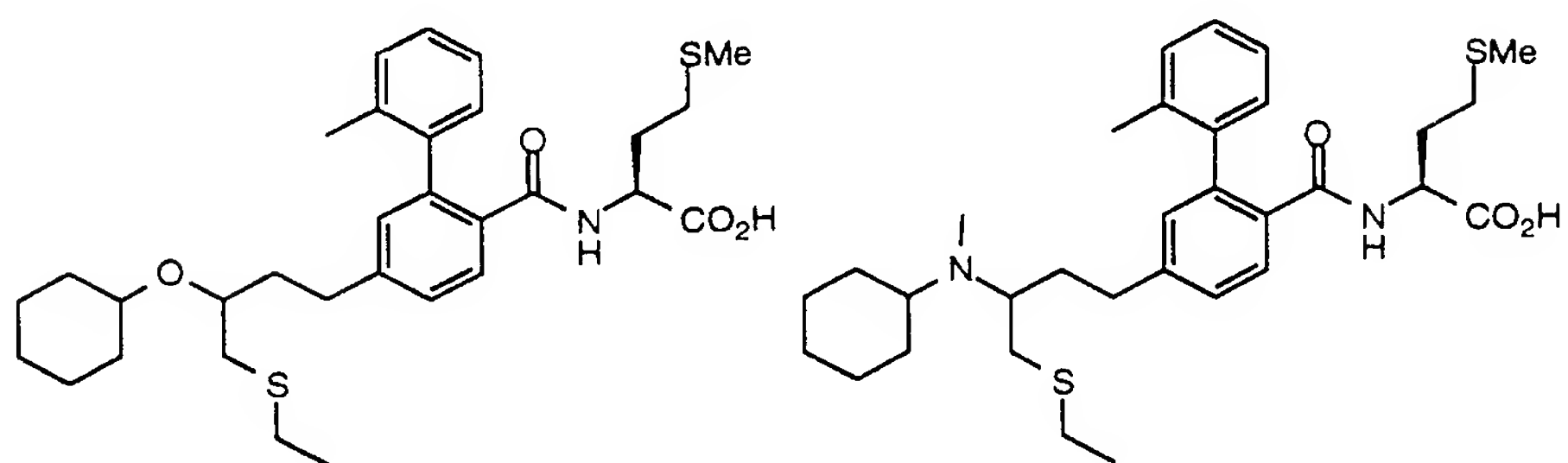
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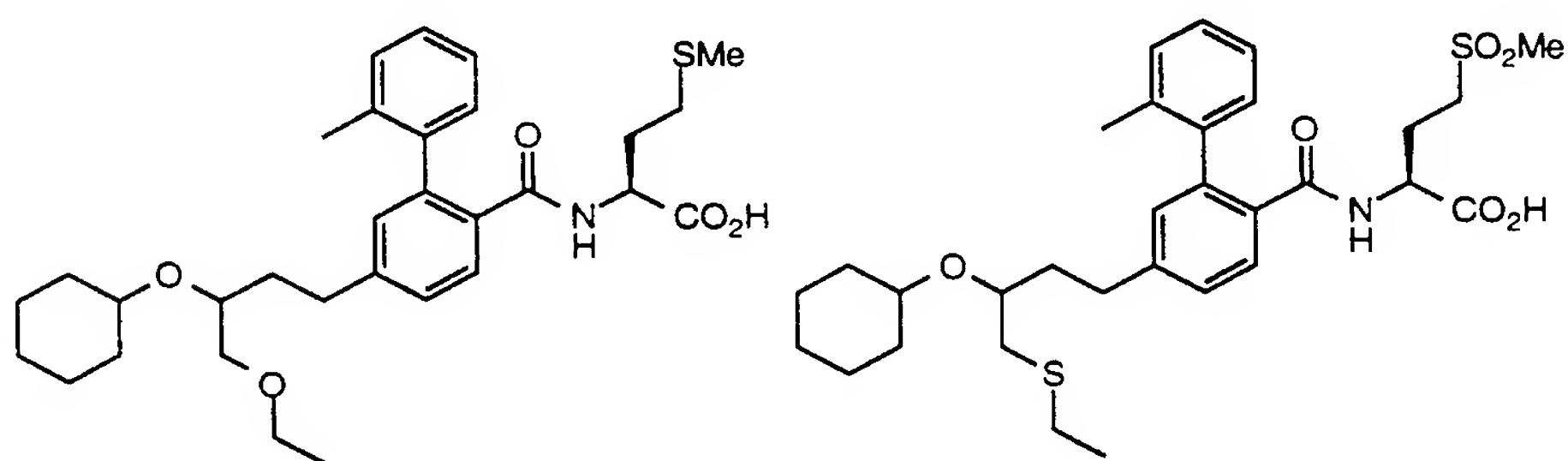


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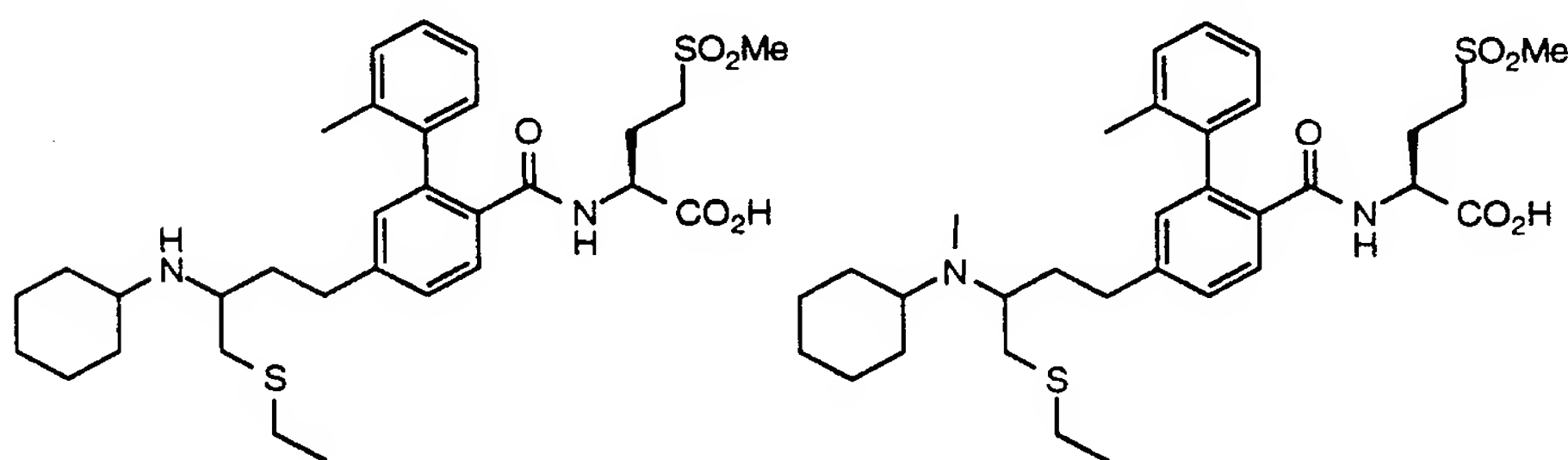
Table 9. Hydrocarbons of the Type A(B)CH<sub>2</sub>-L<sub>1</sub>

1 2

2495

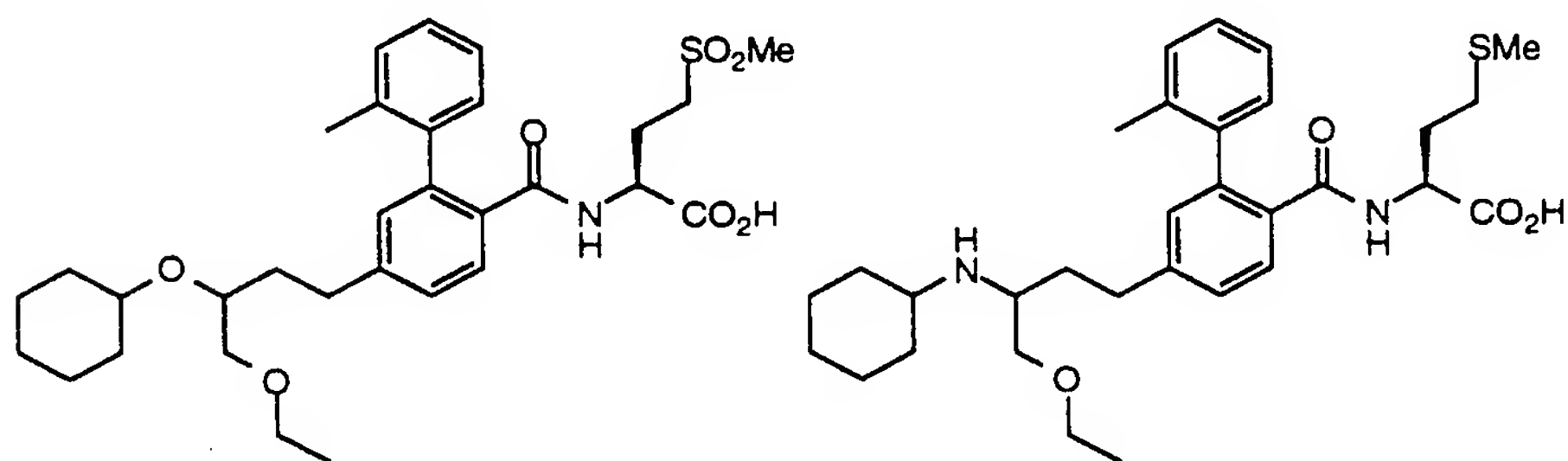


3 4



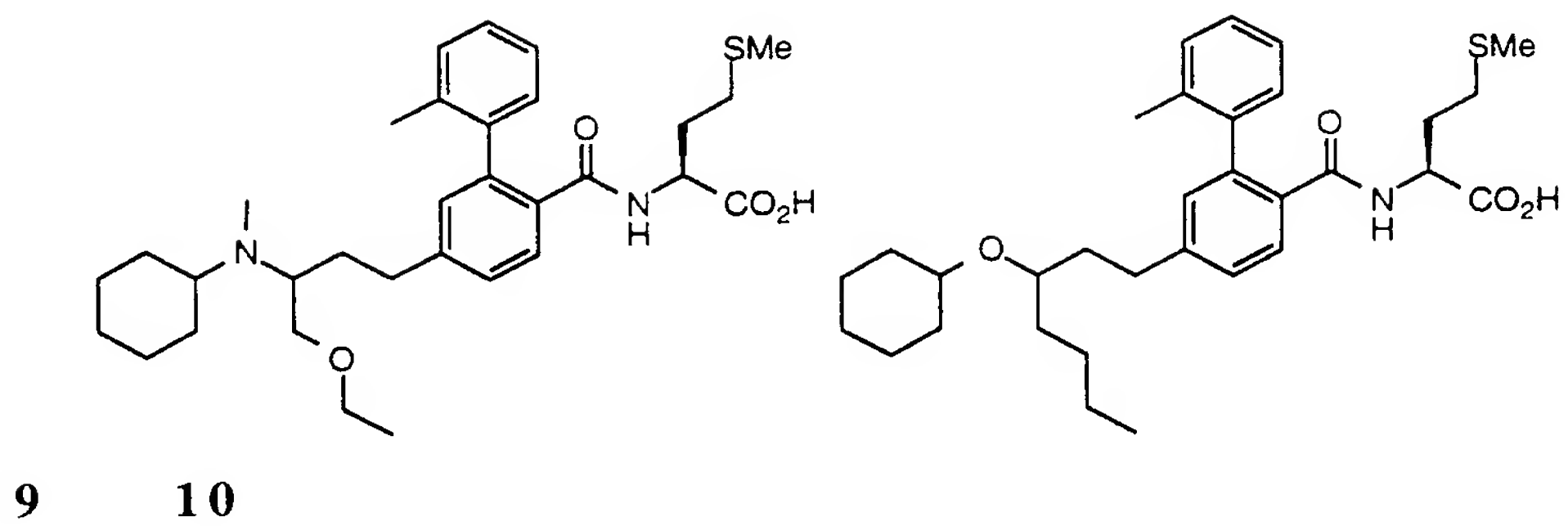
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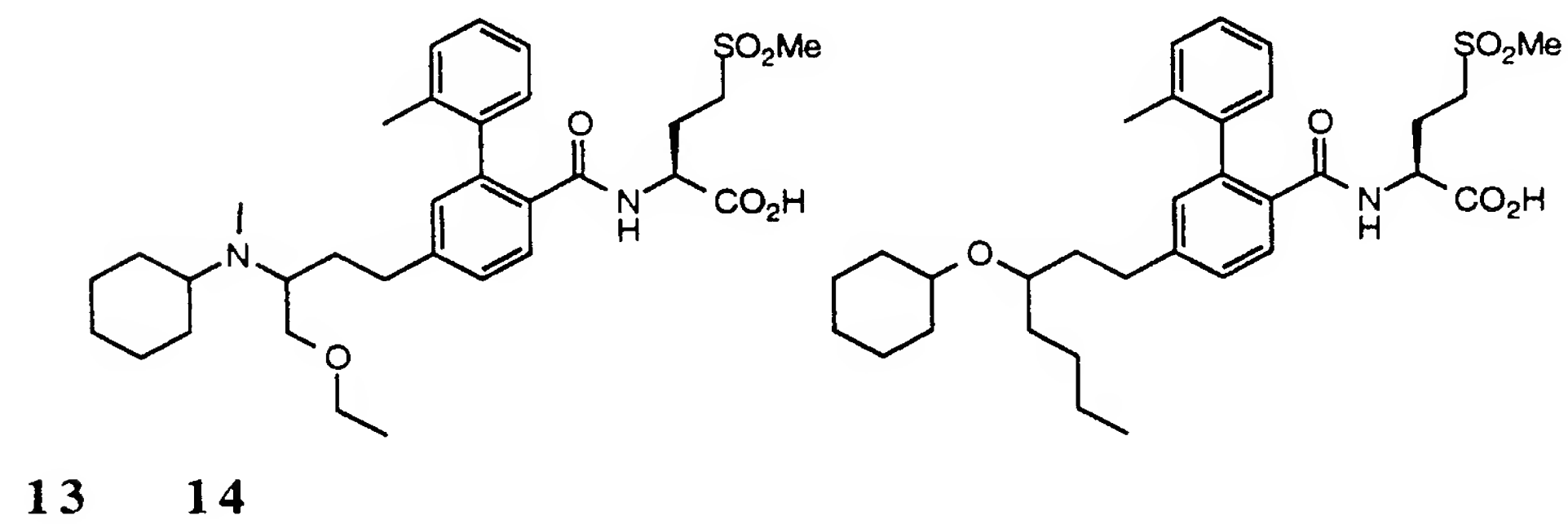
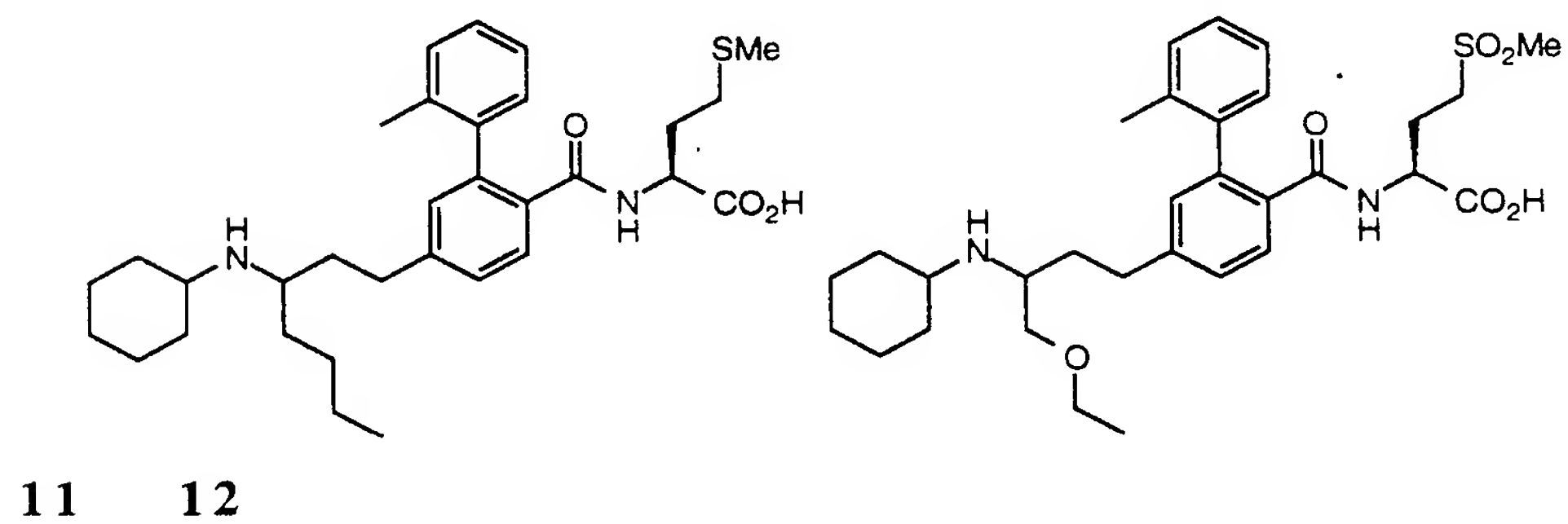


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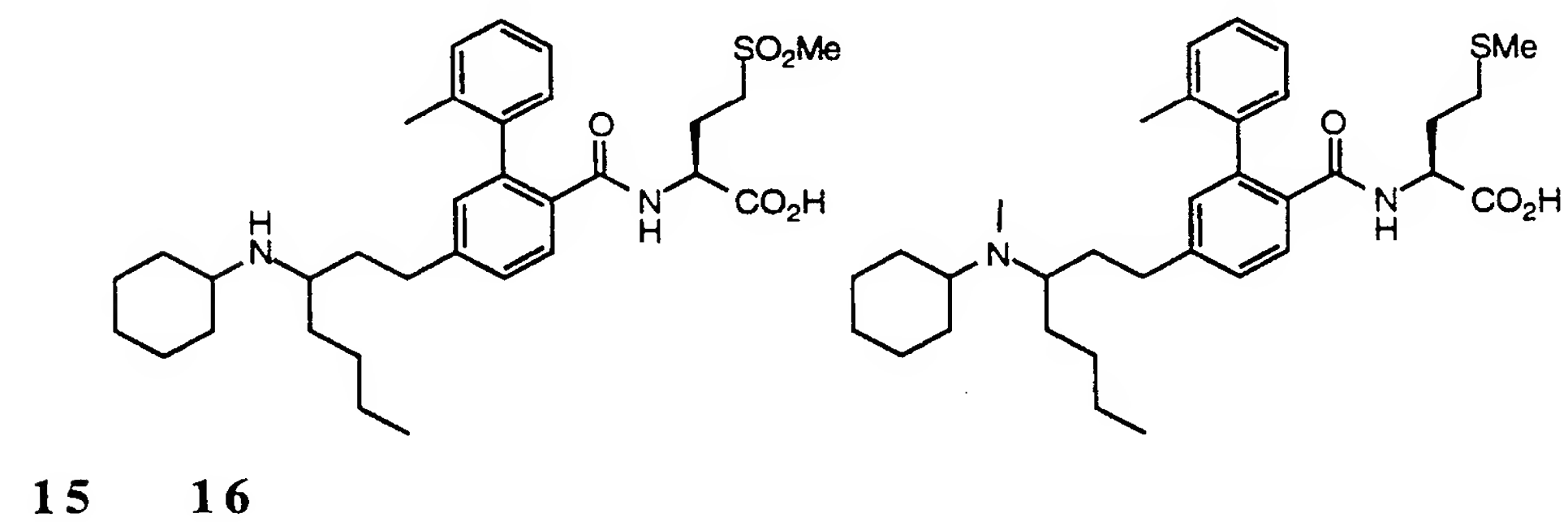
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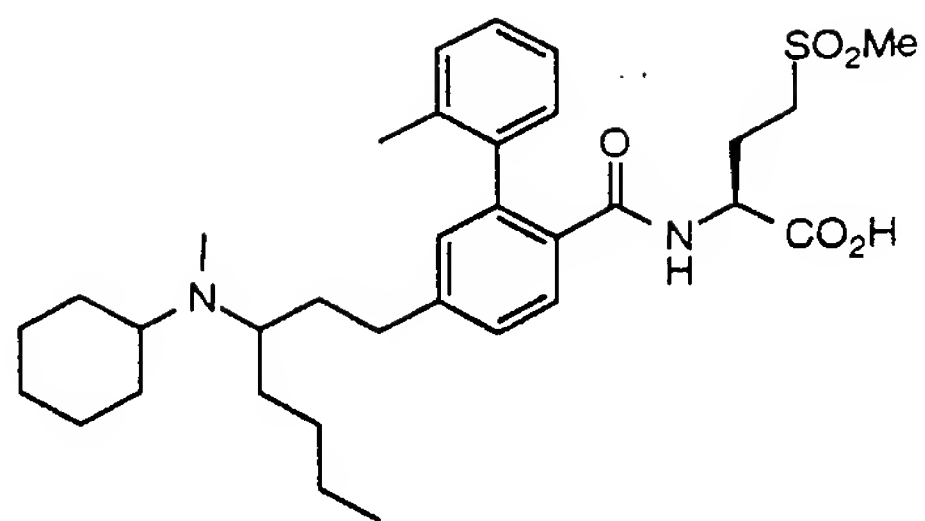


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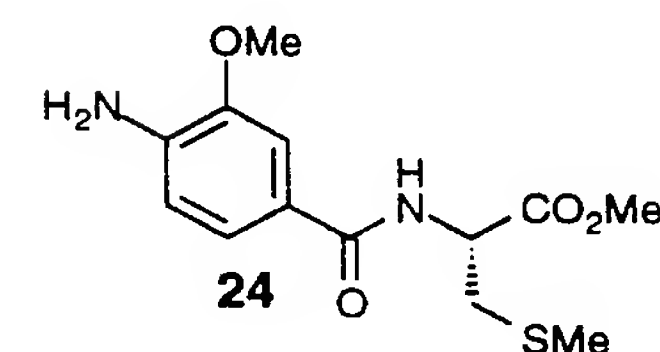
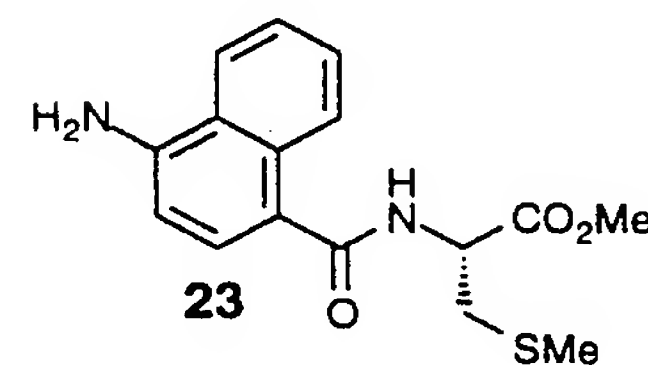
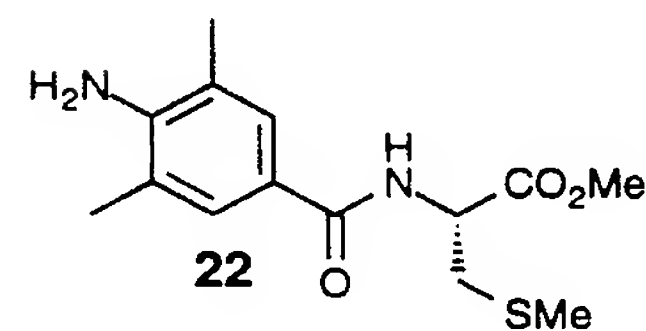
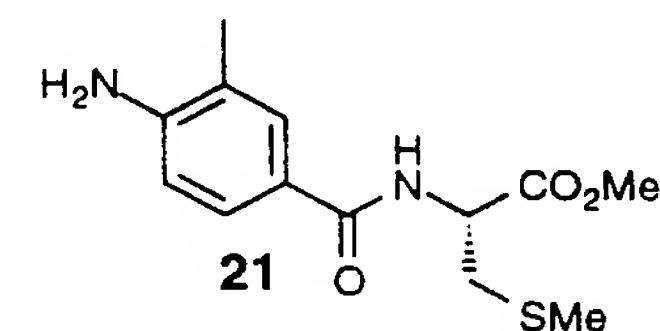
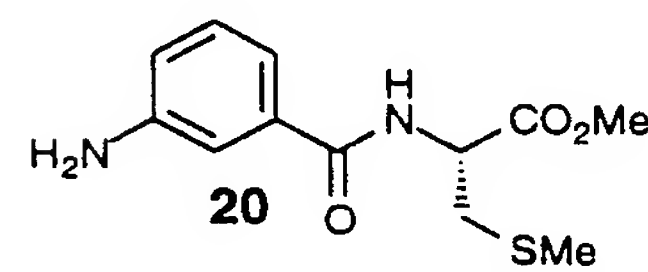
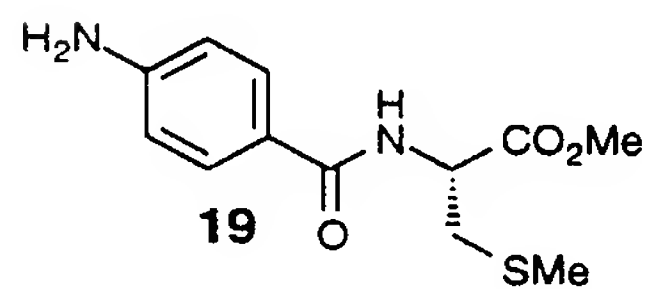
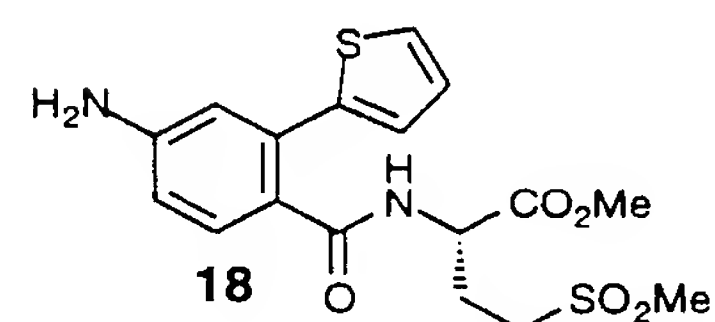
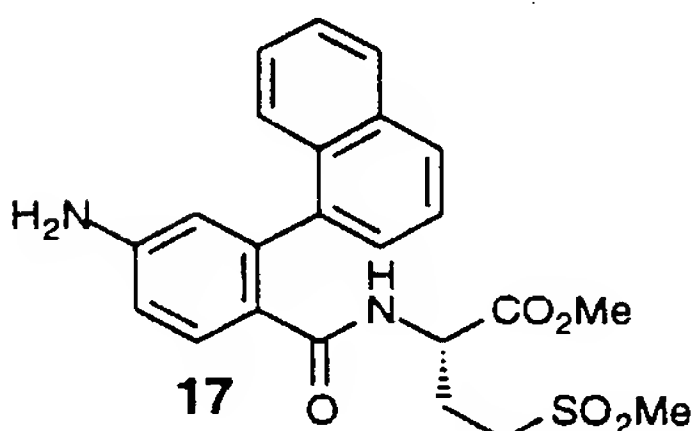
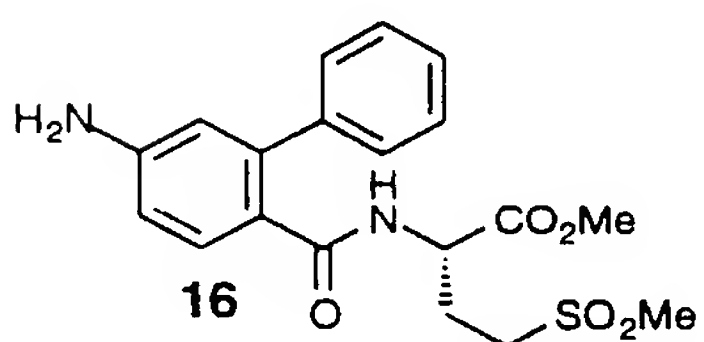
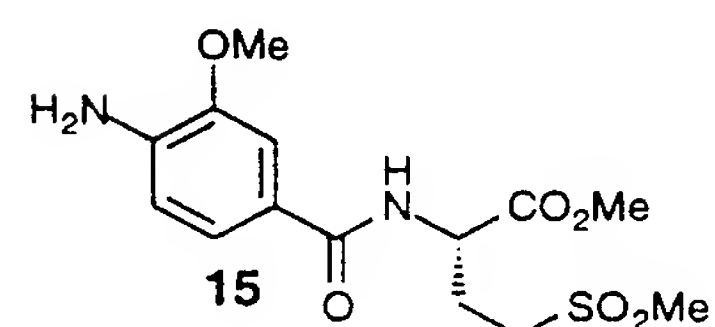
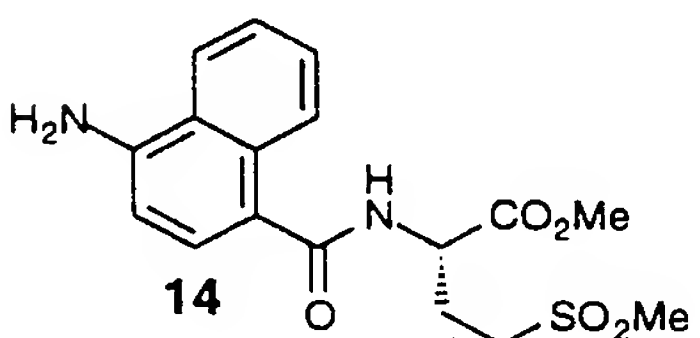
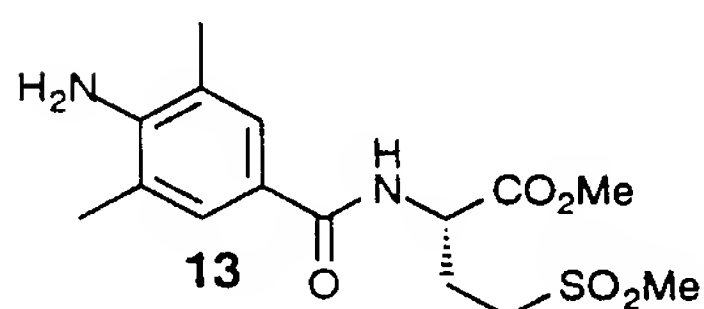
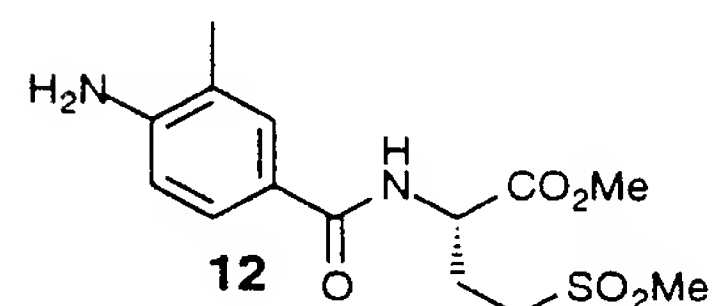
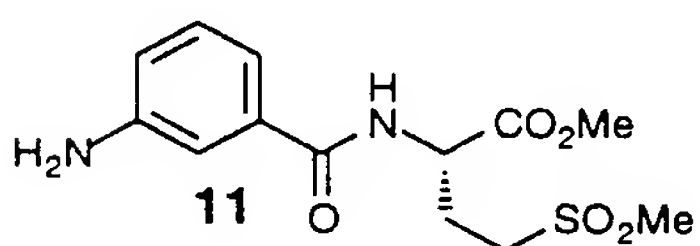
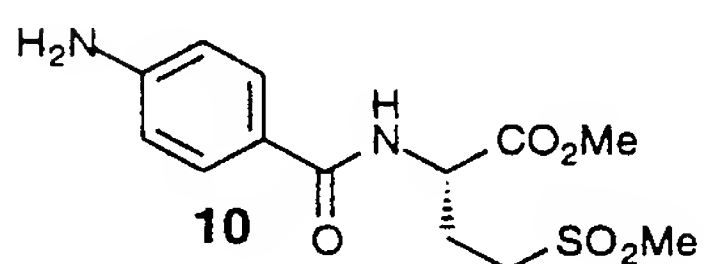
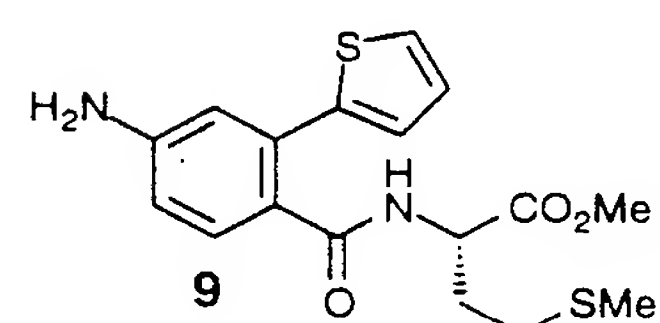
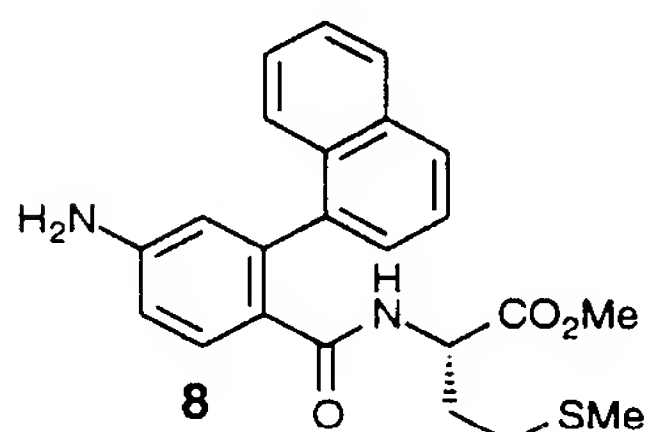
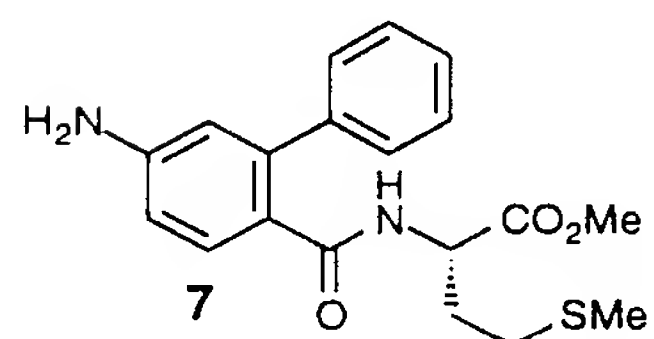
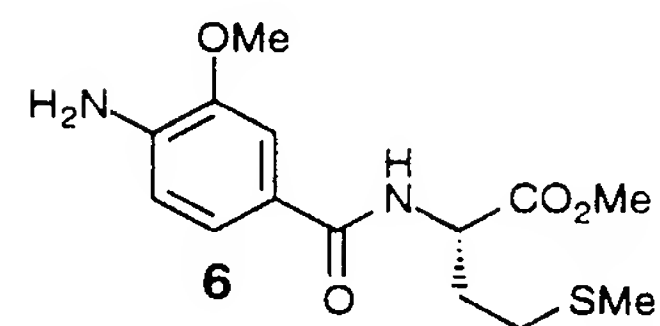
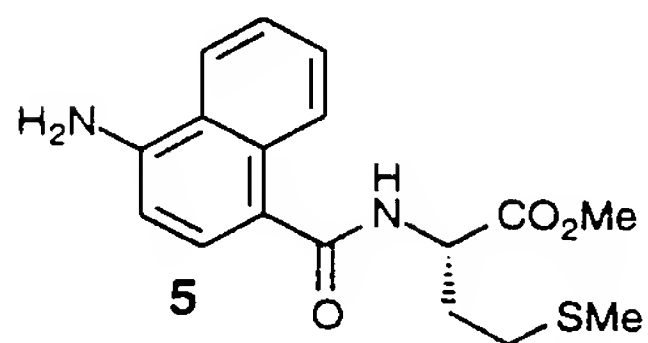
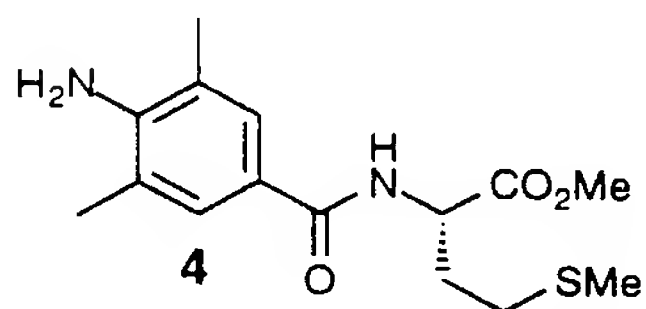
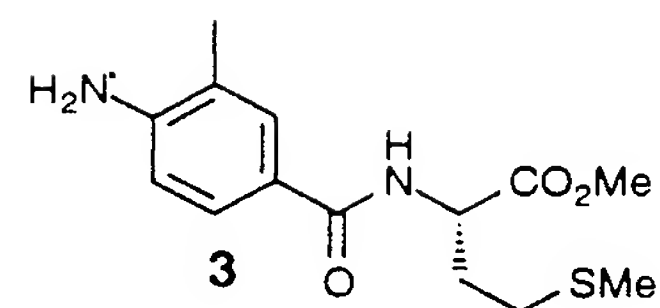
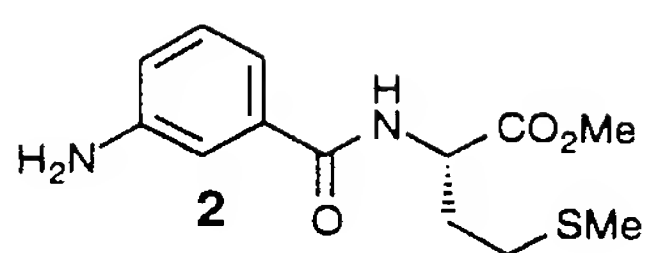
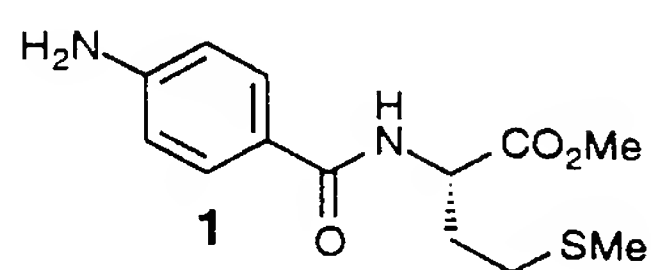


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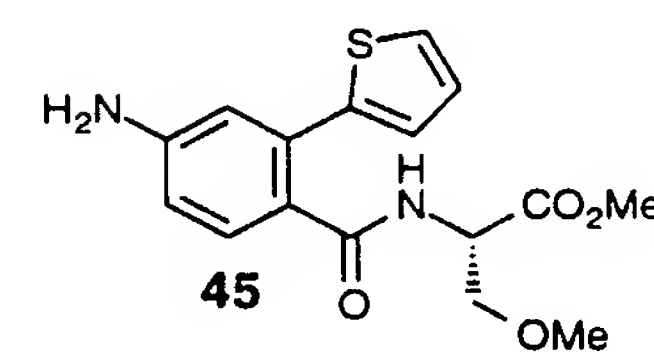
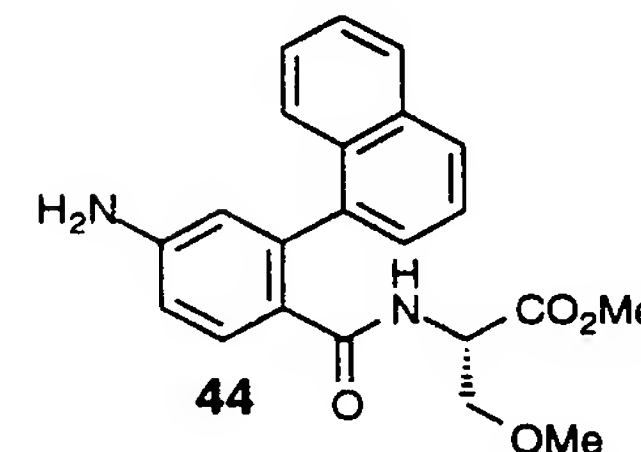
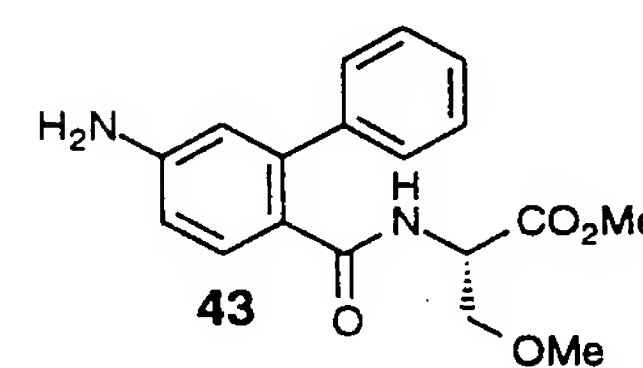
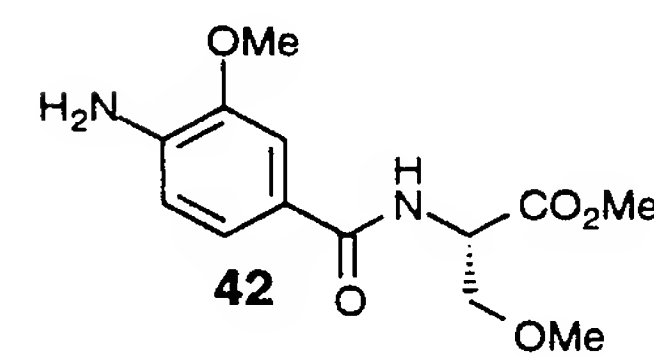
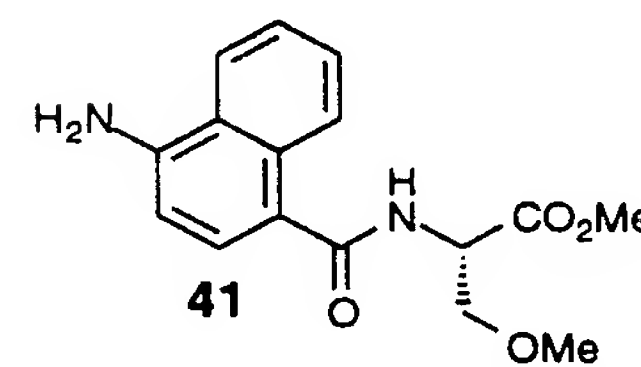
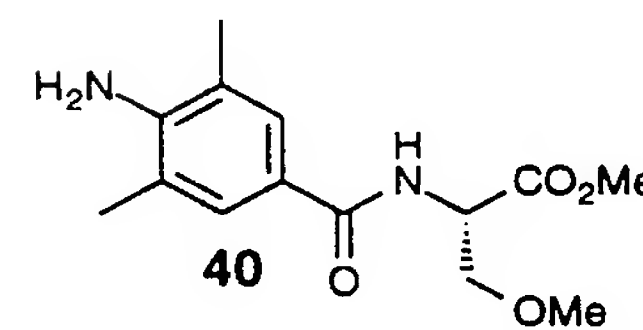
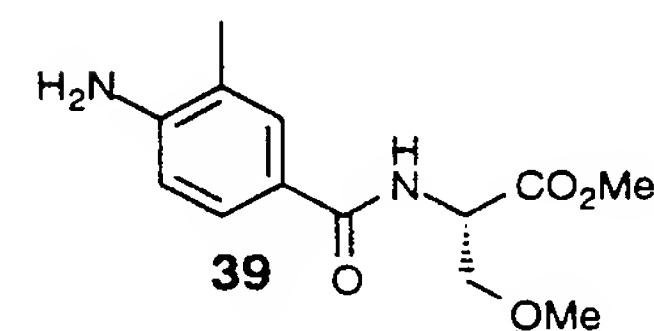
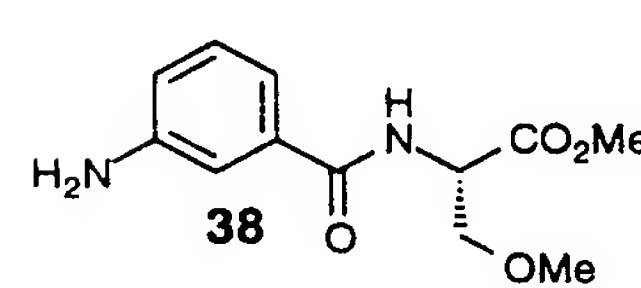
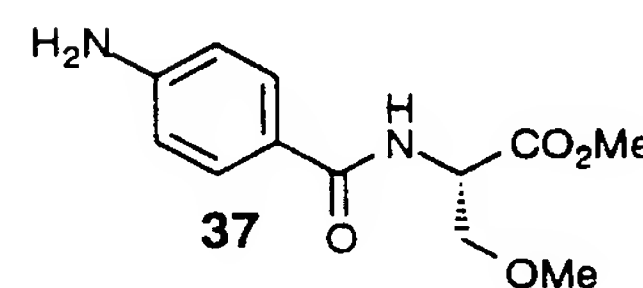
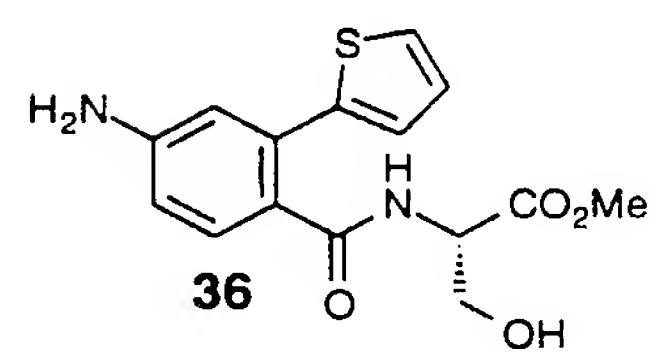
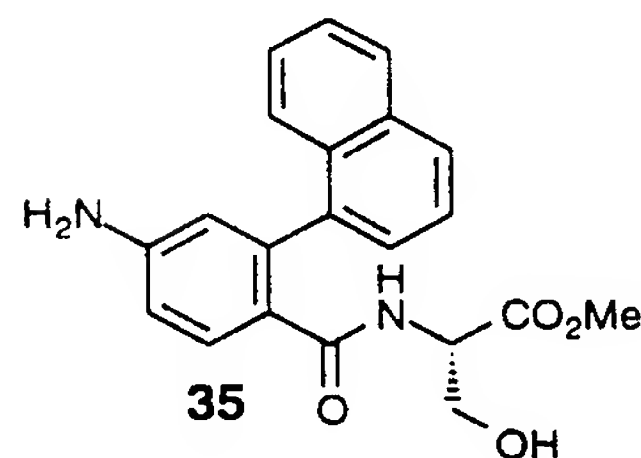
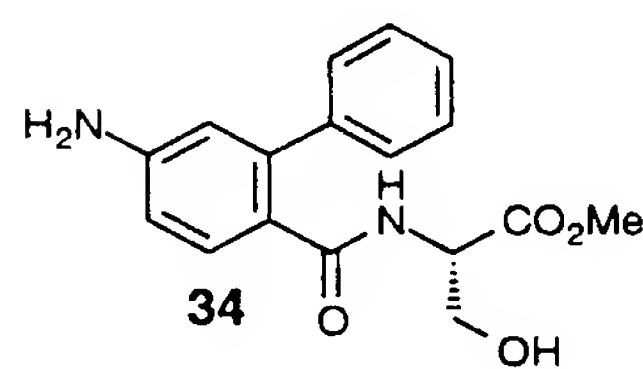
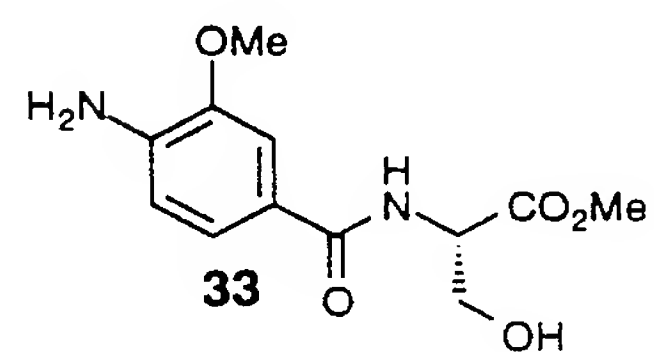
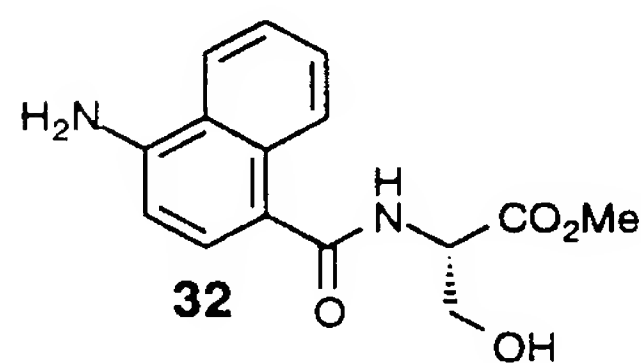
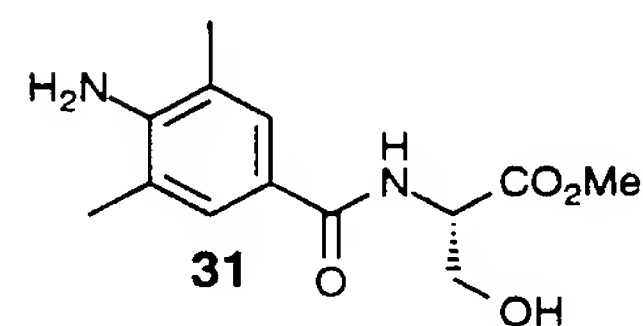
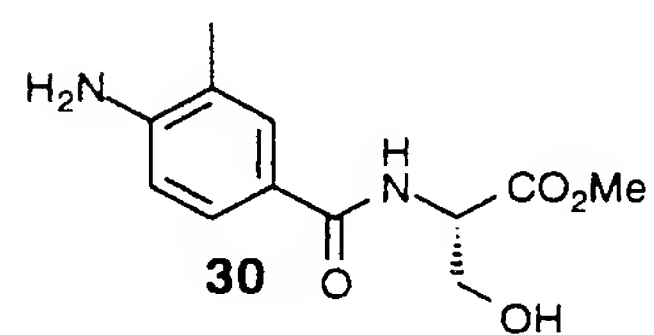
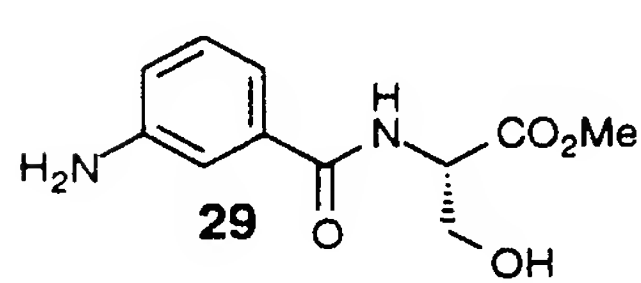
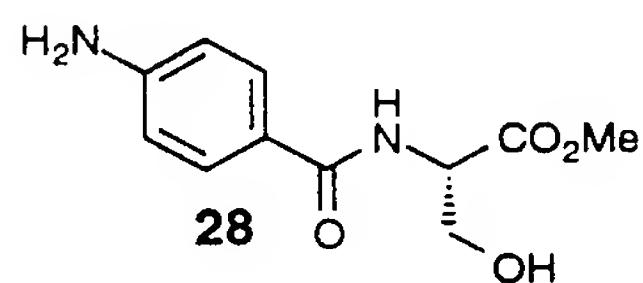
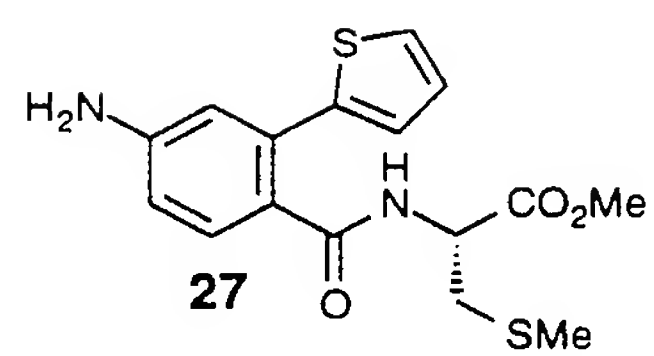
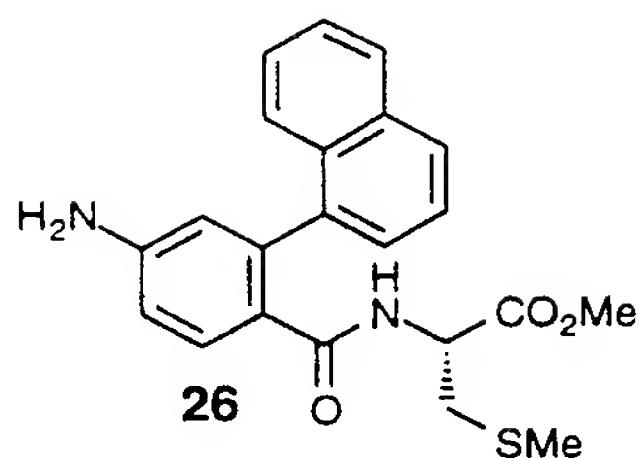
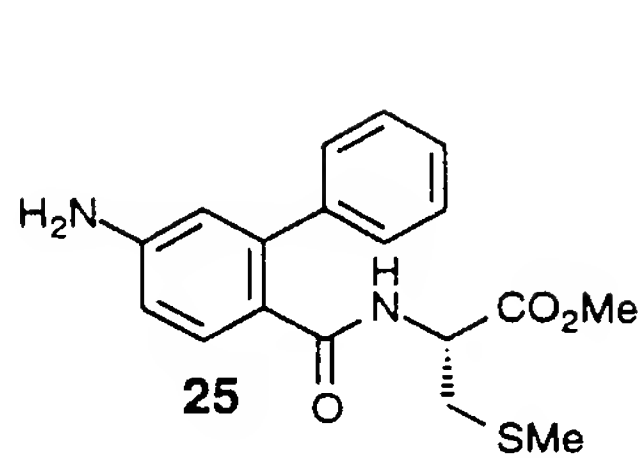




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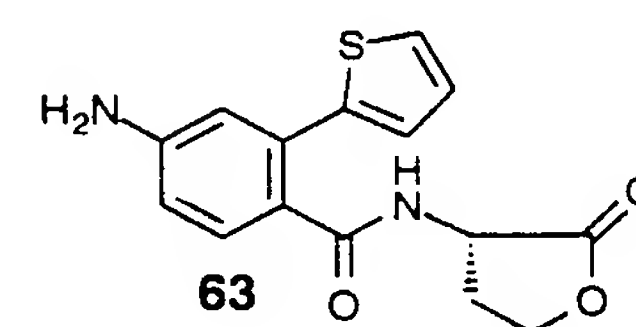
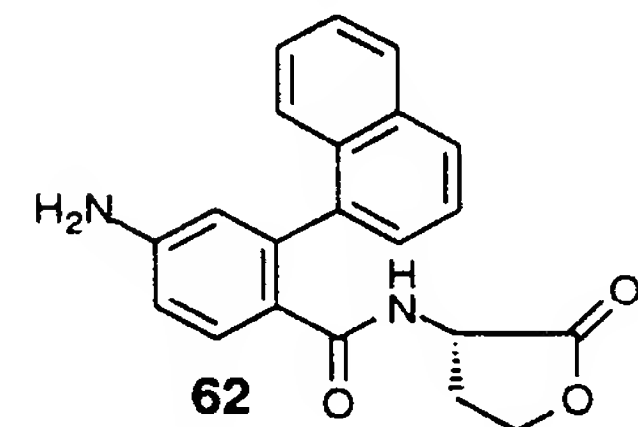
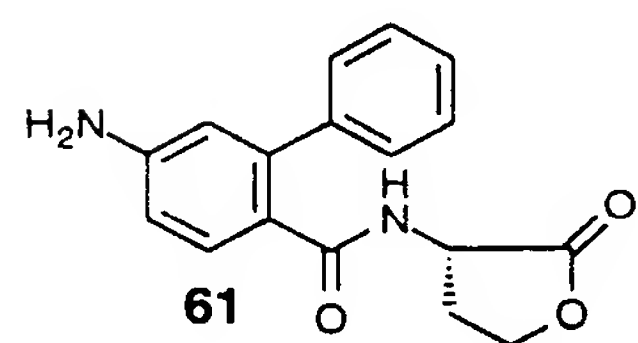
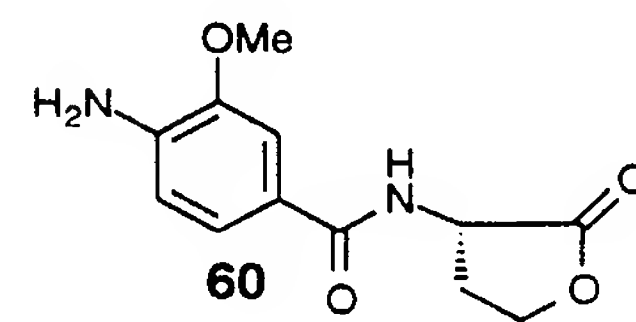
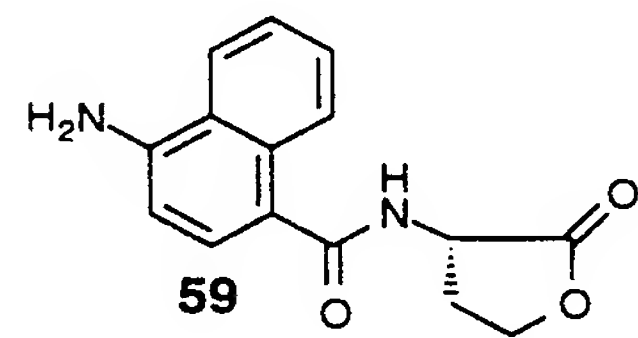
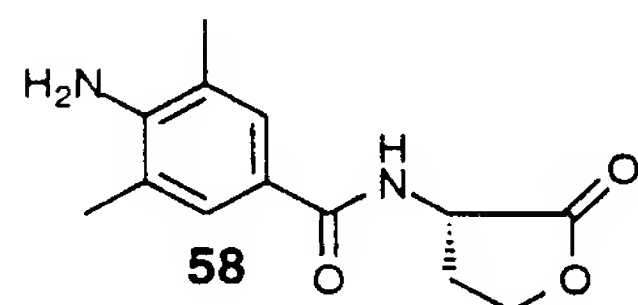
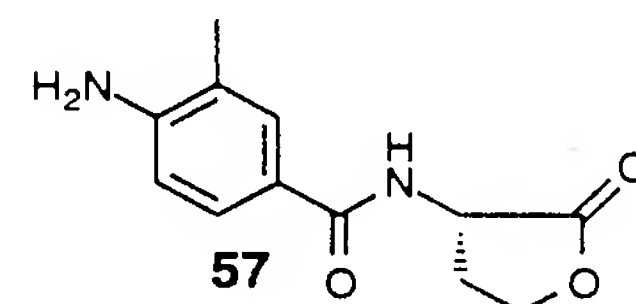
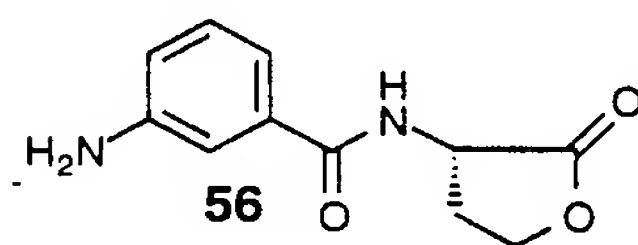
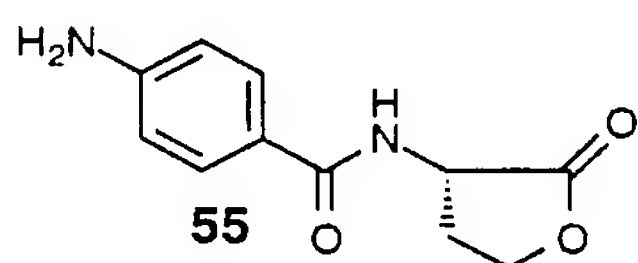
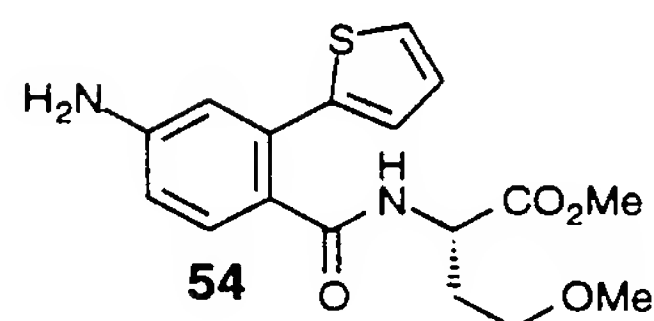
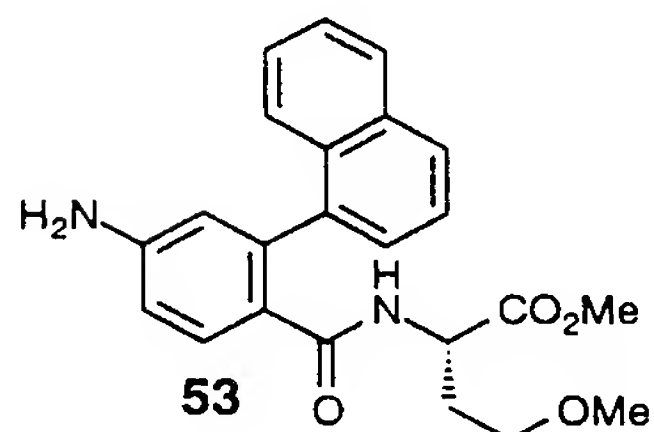
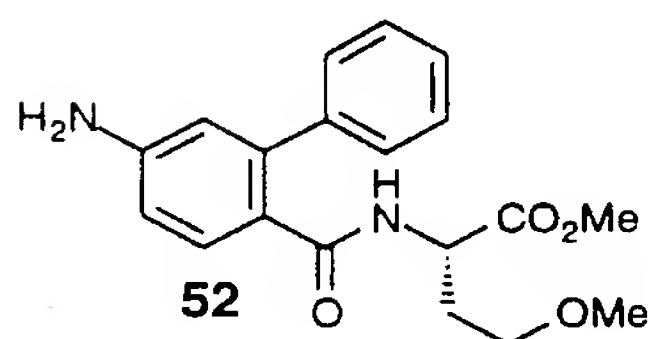
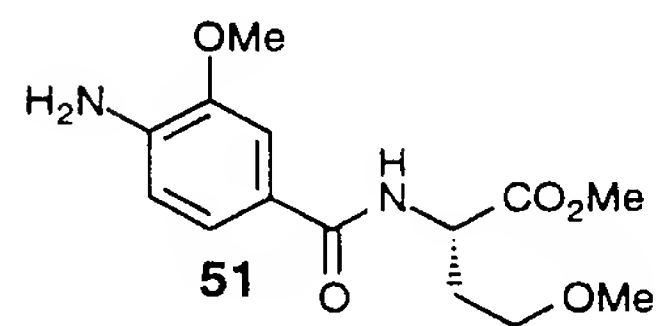
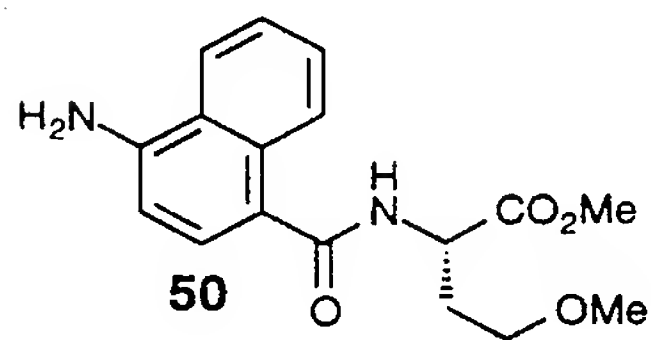
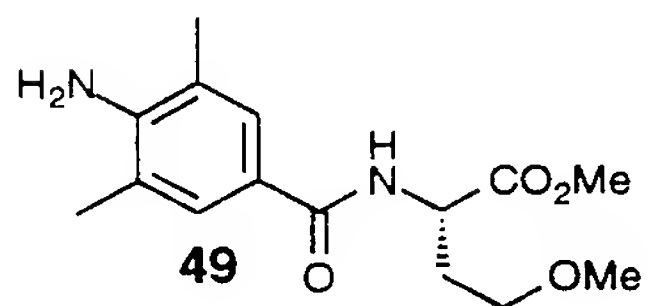
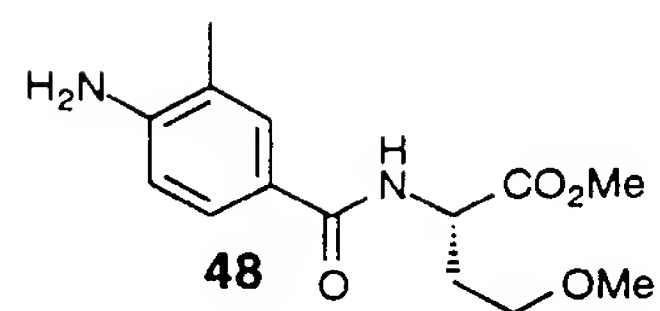
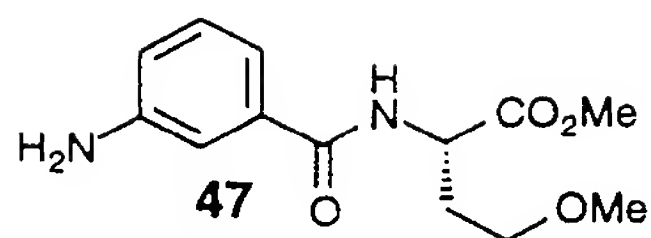
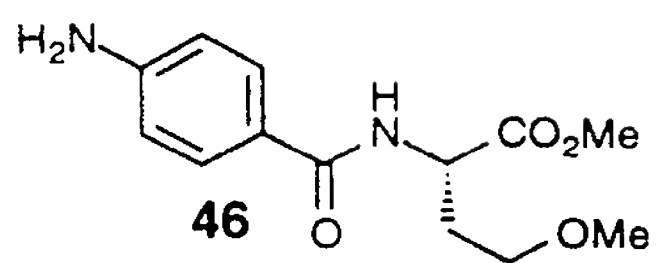
Table 10. Amines of the type B-NH<sub>2</sub>



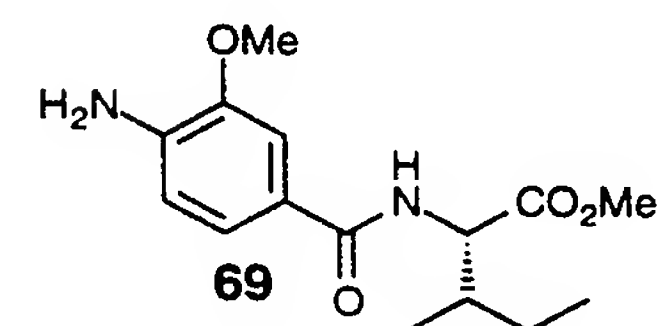
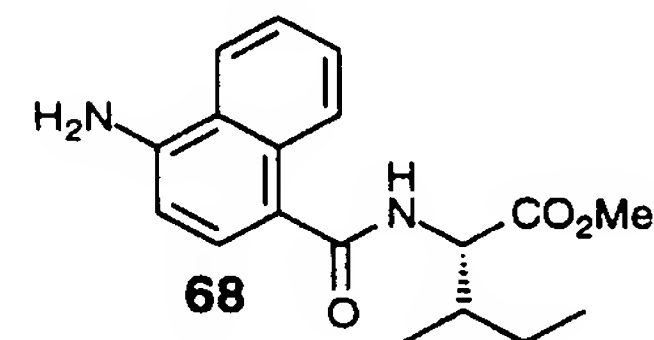
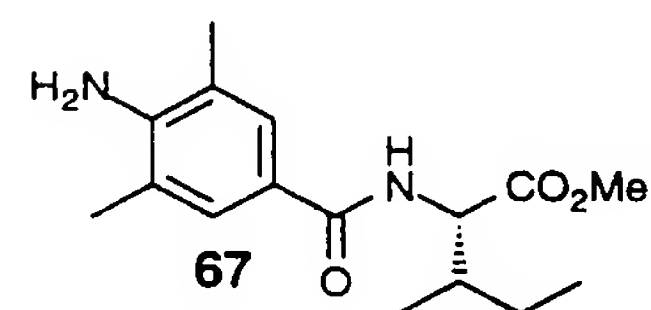
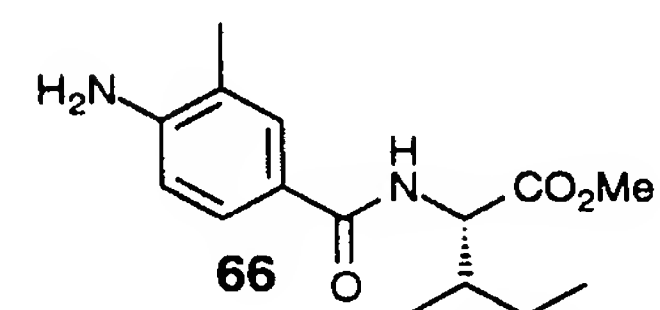
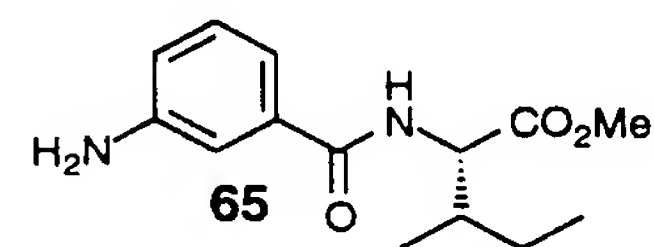
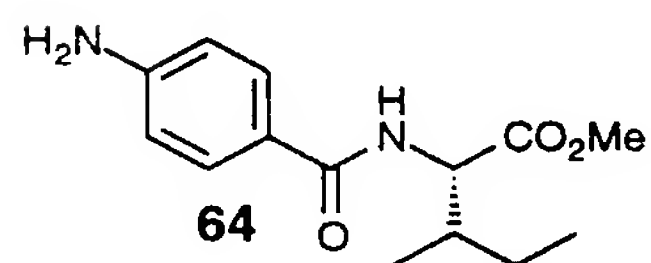


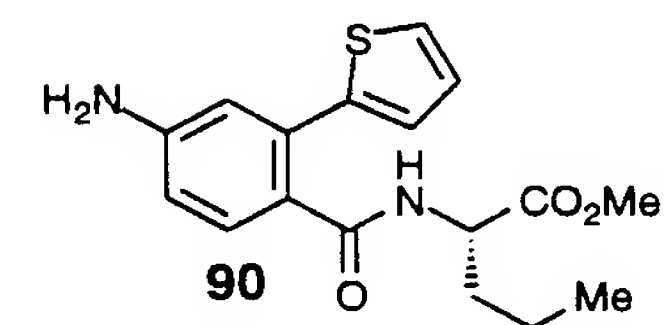
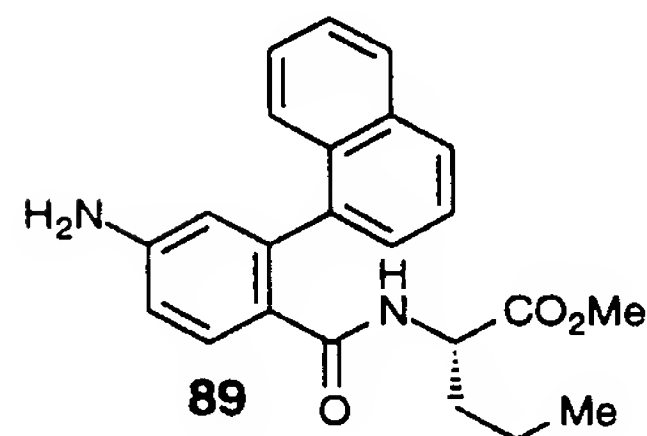
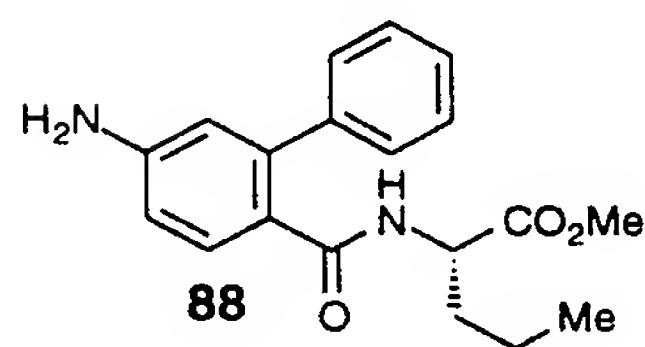
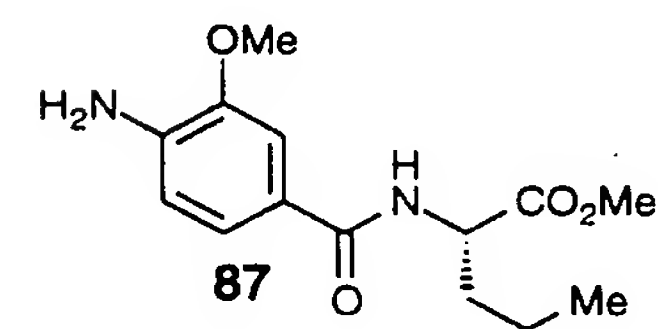
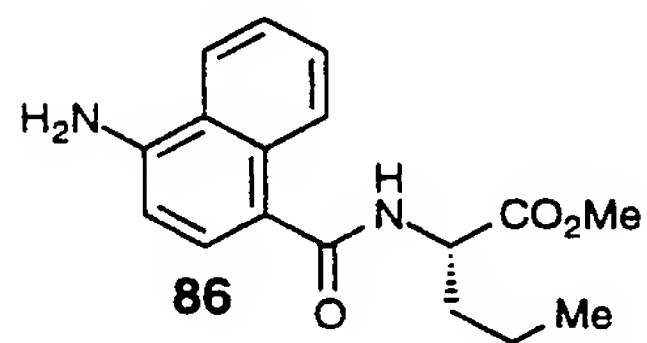
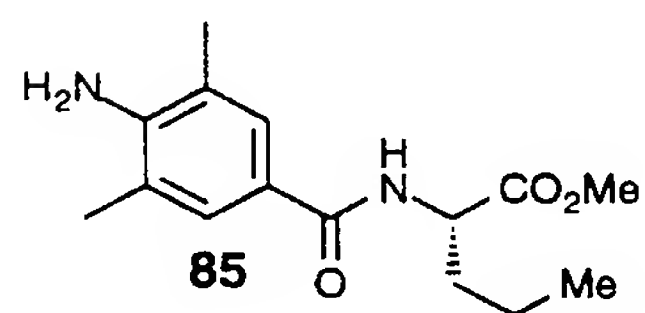
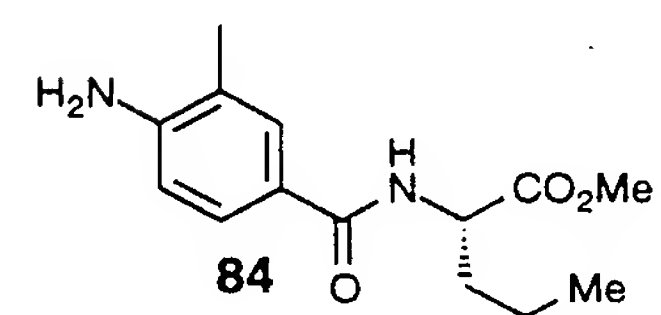
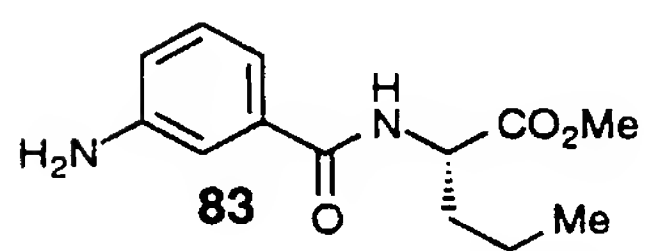
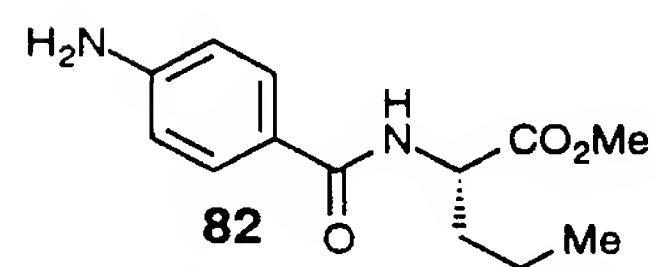
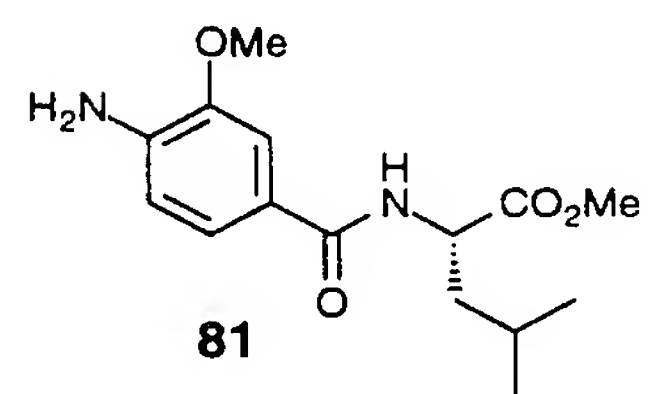
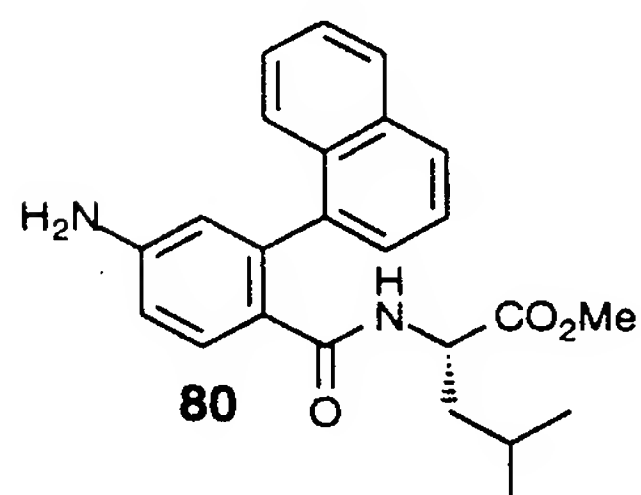
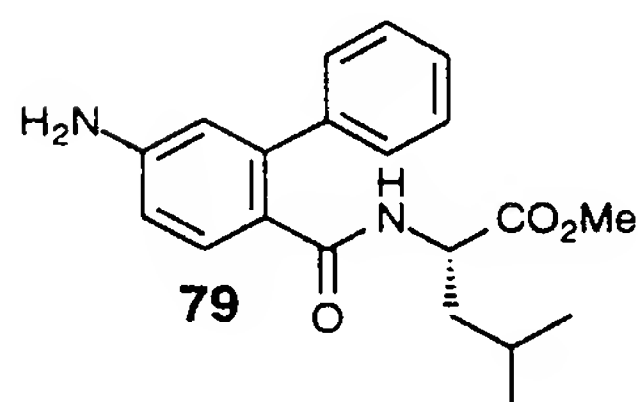
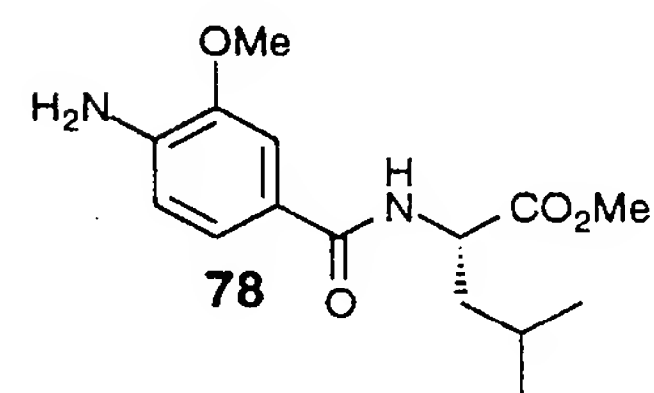
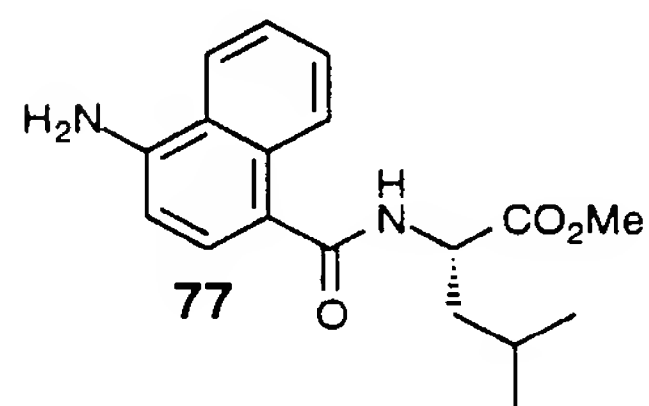
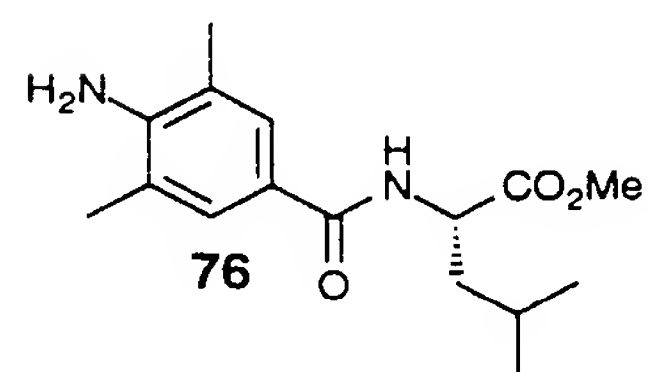
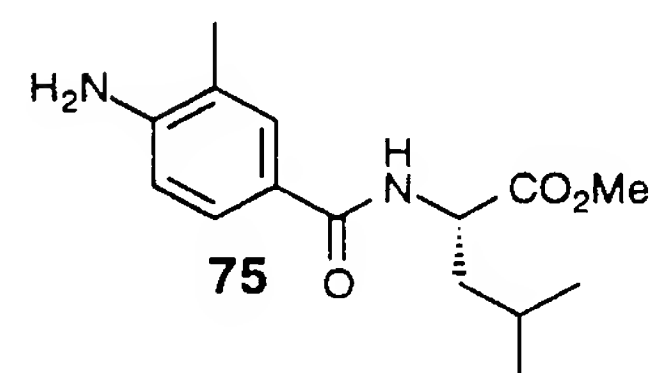
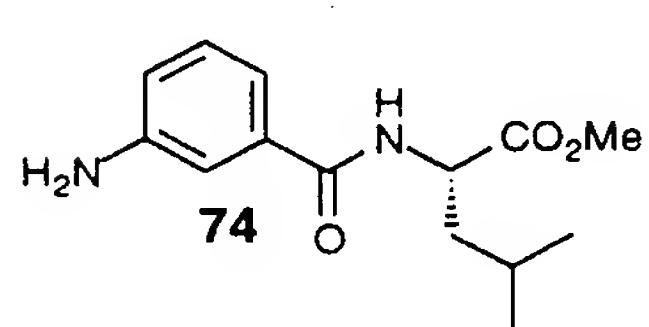
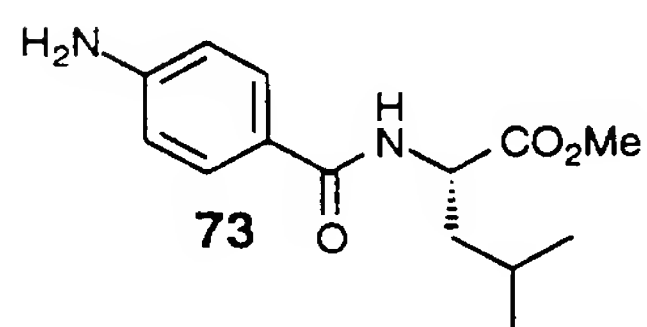
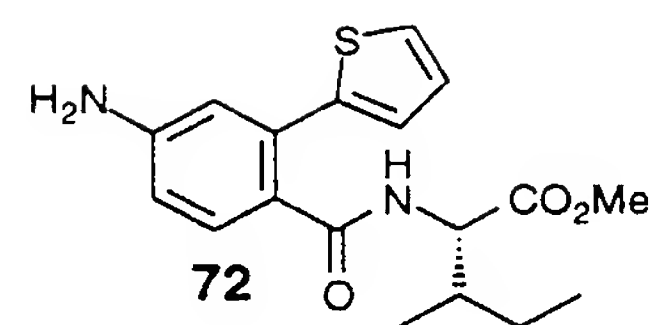
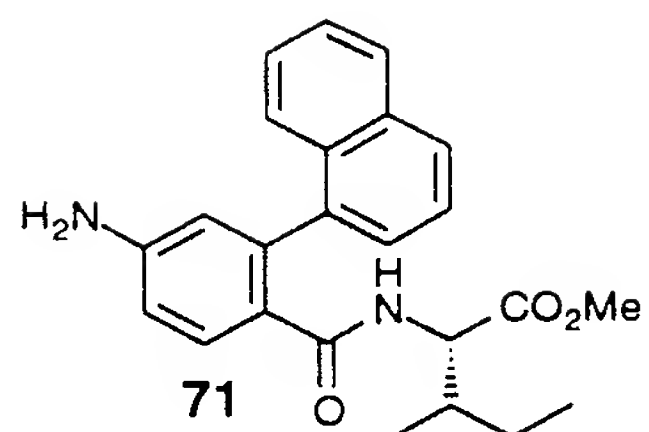
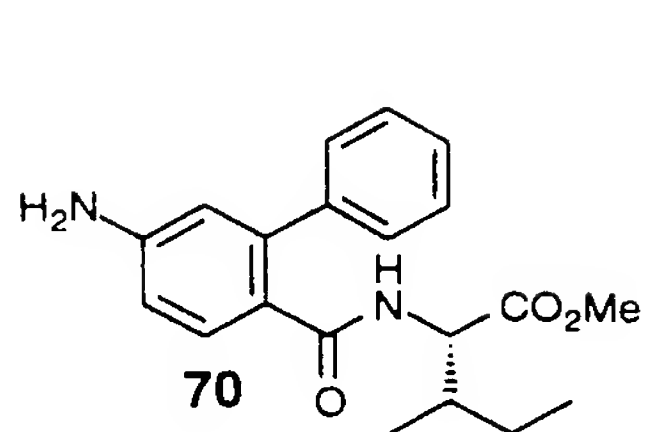
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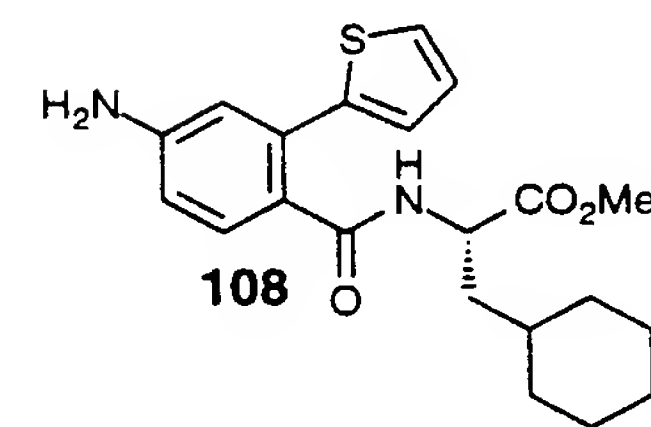
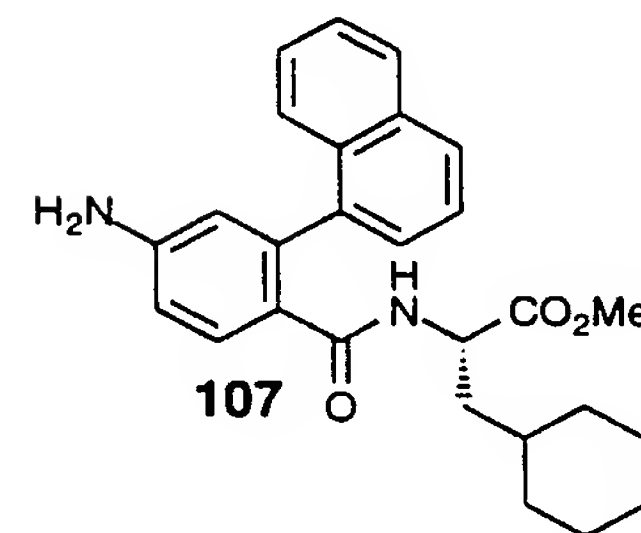
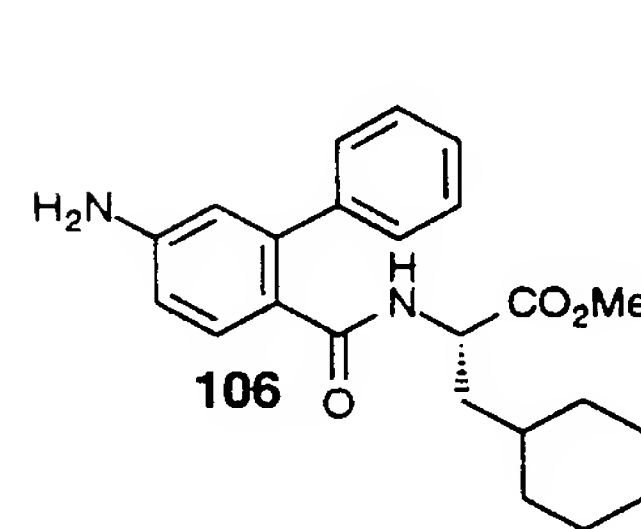
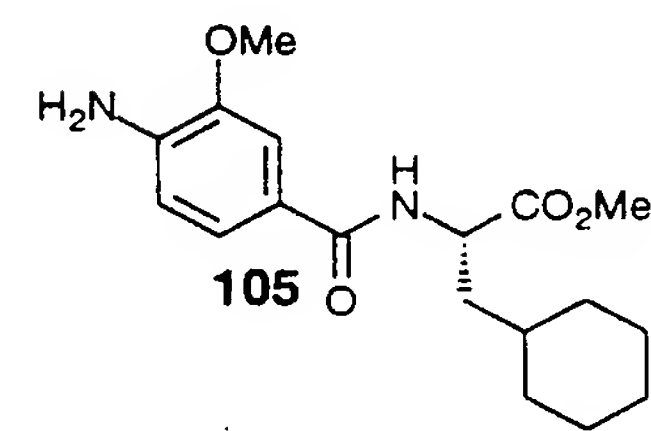
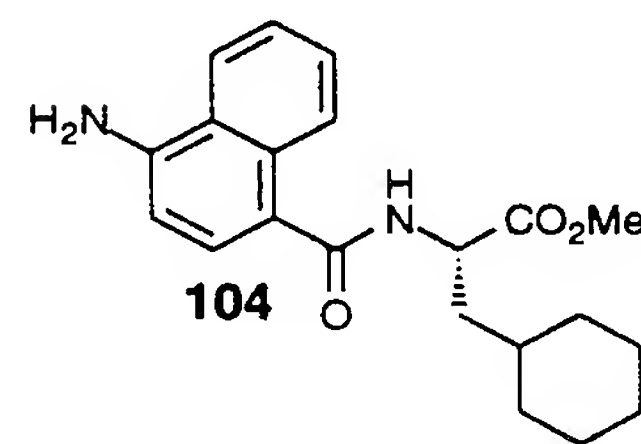
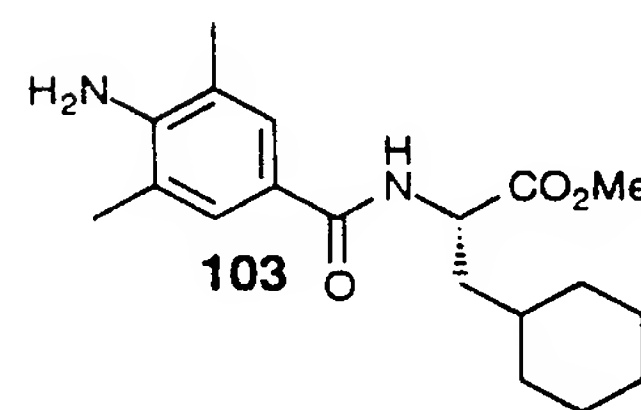
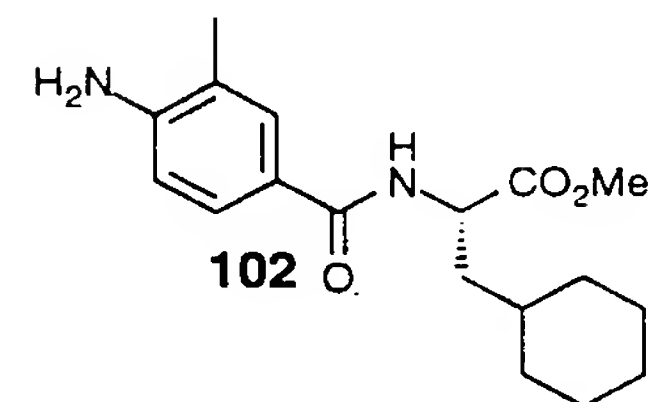
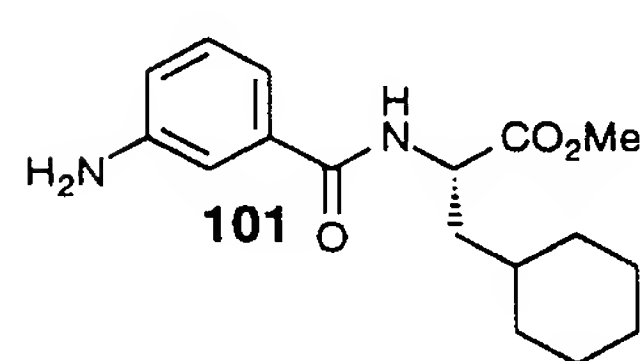
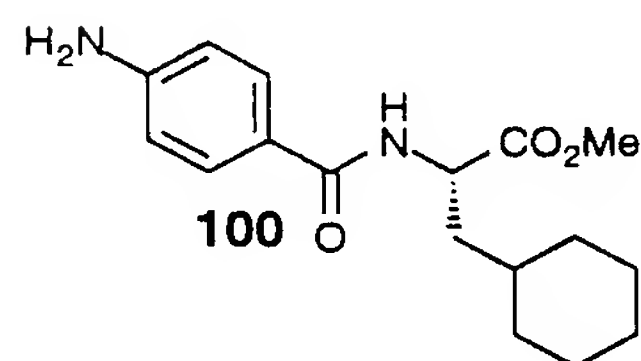
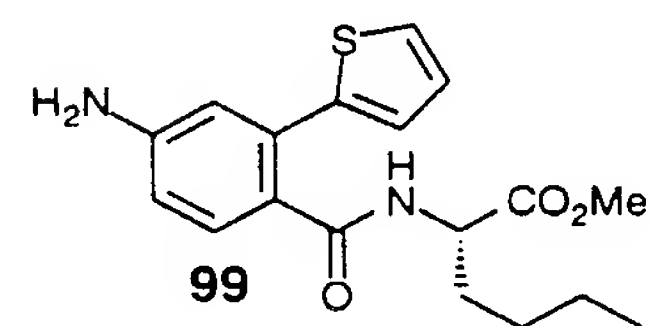
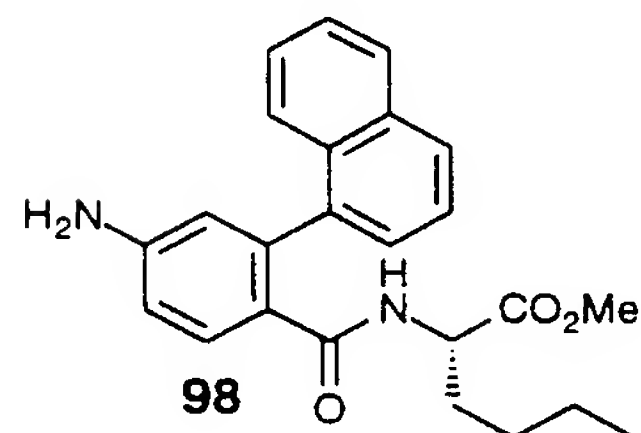
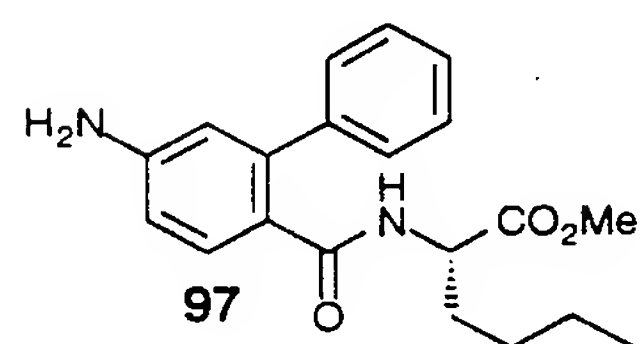
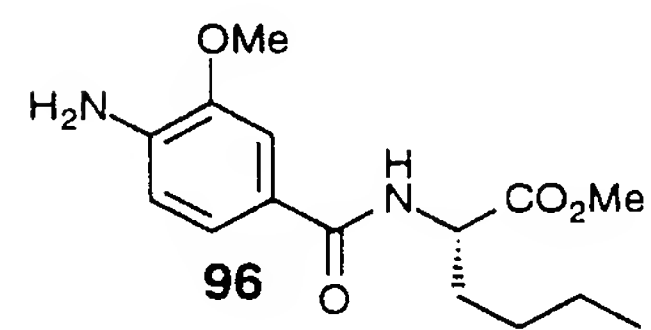
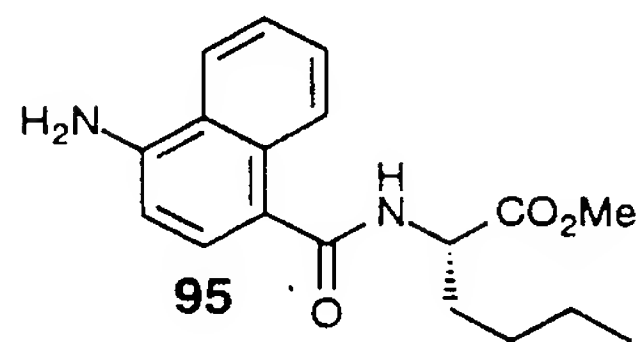
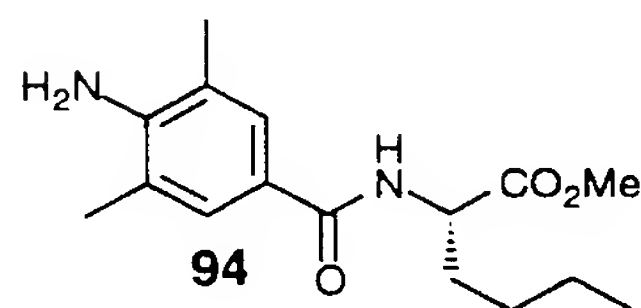
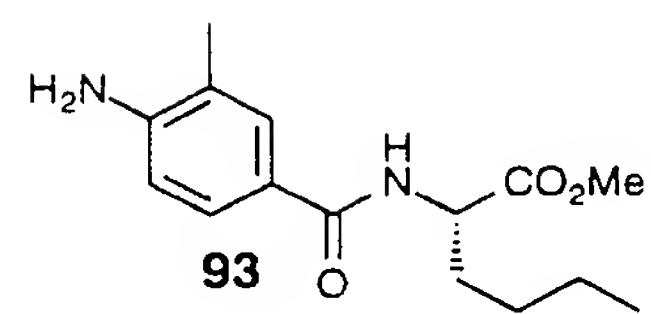
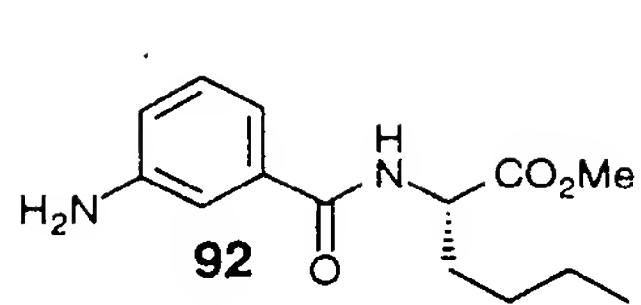
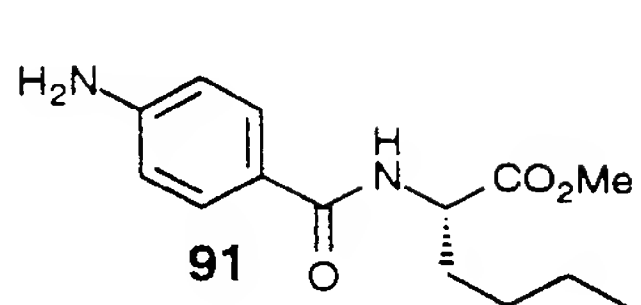


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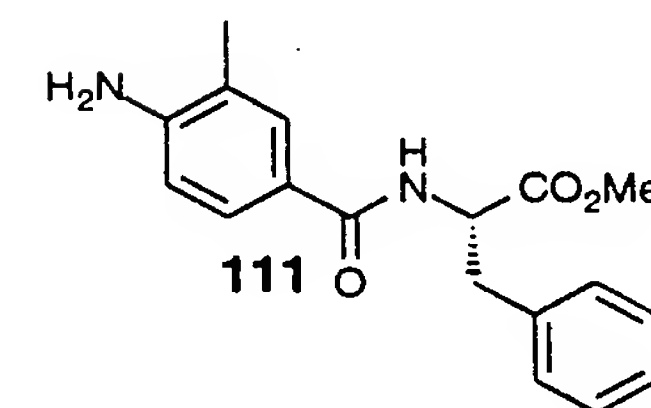
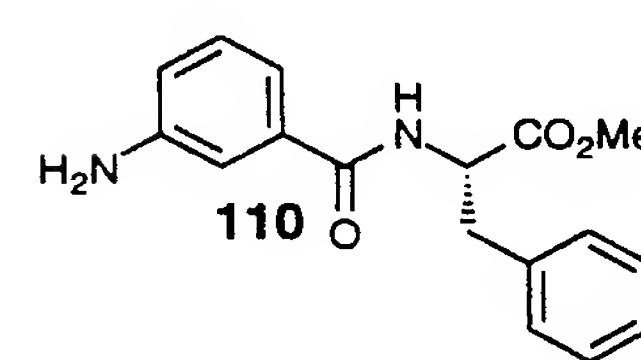
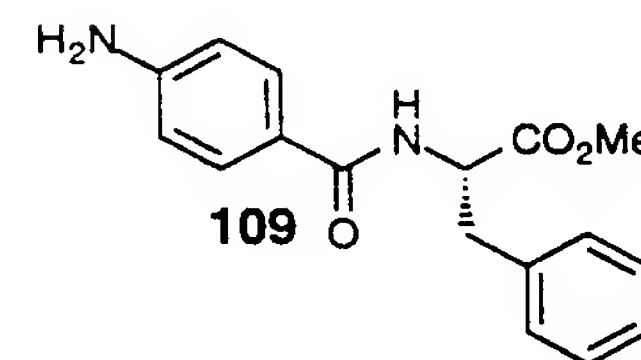


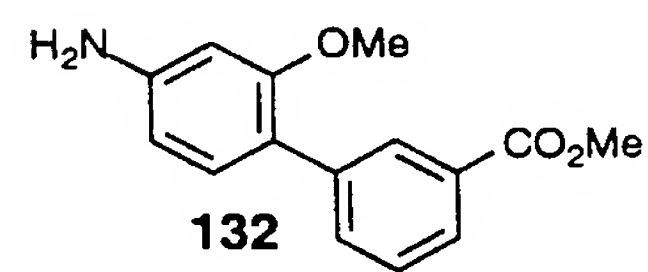
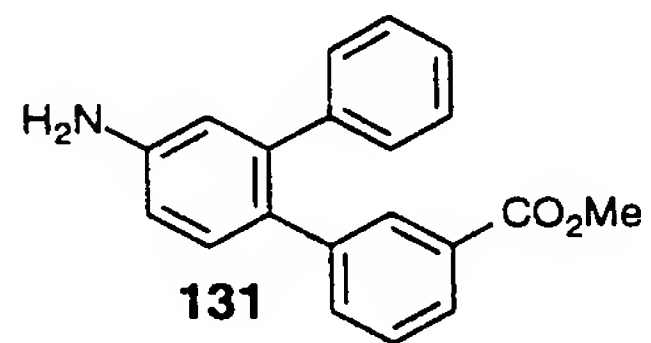
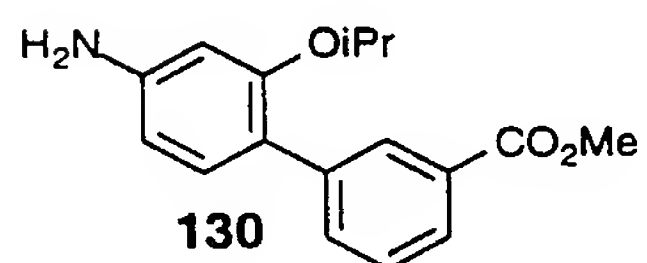
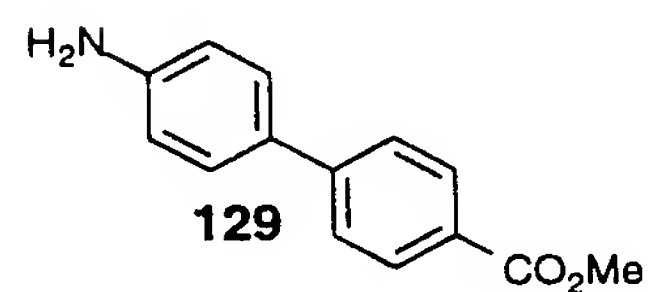
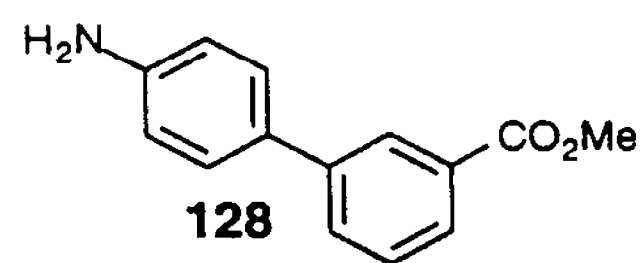
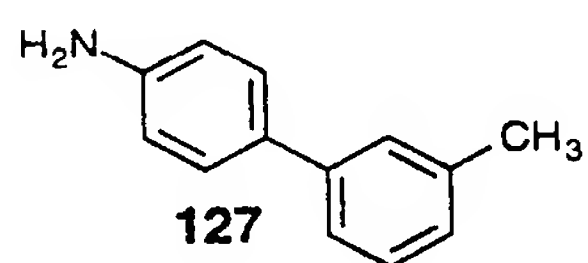
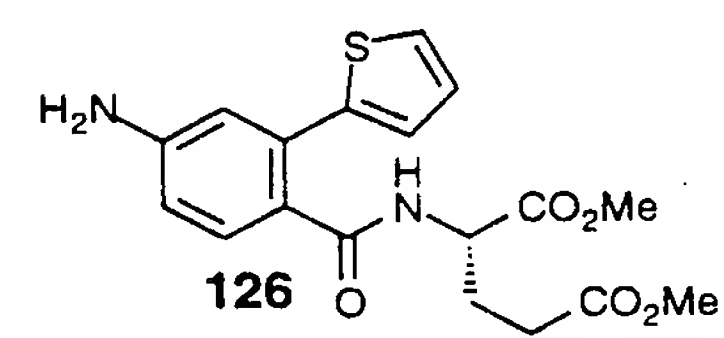
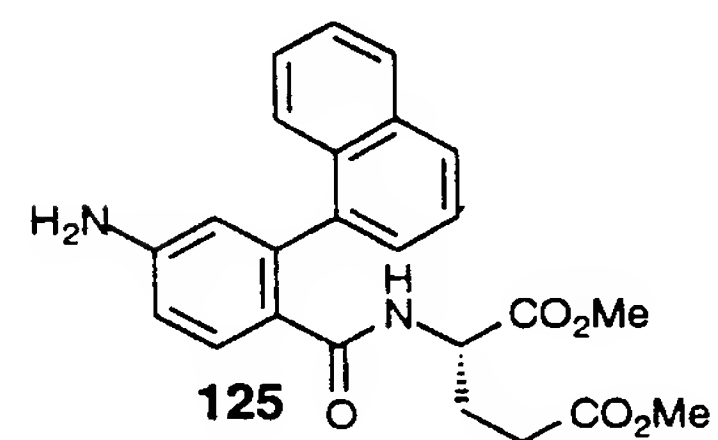
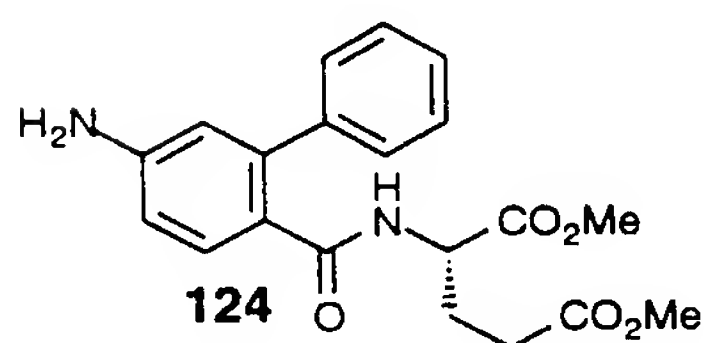
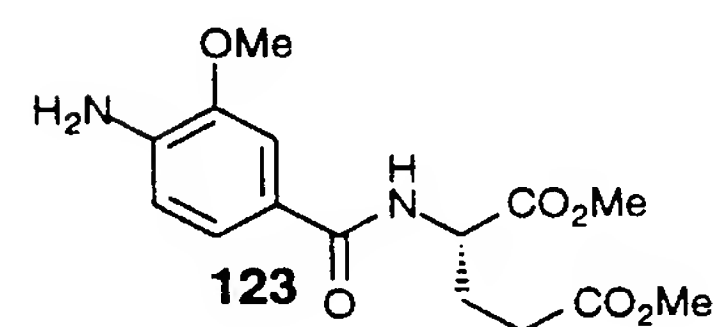
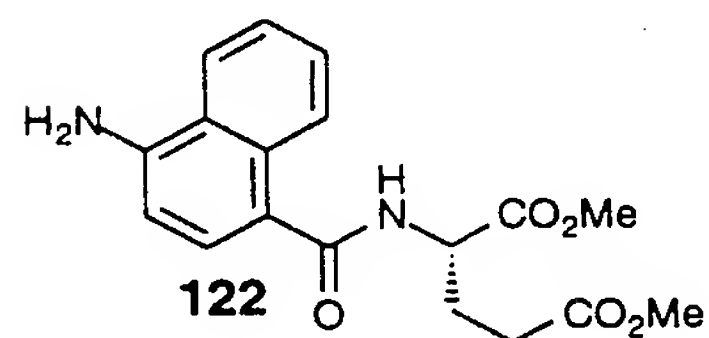
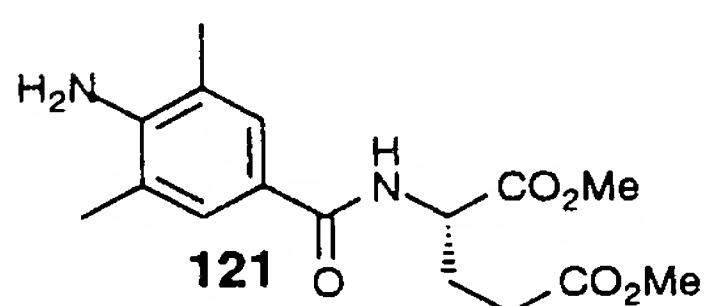
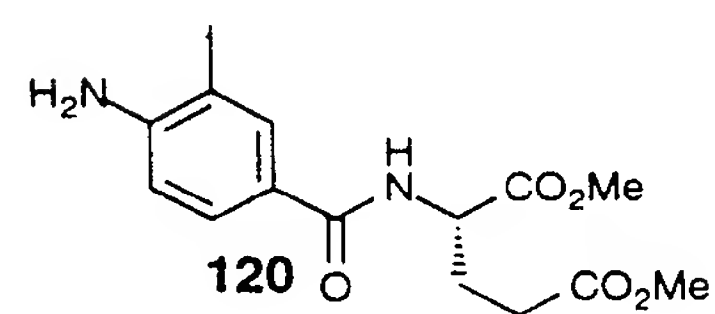
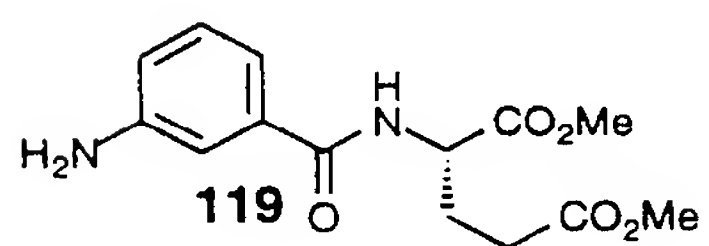
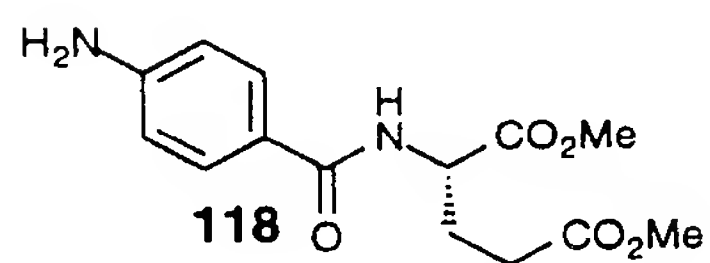
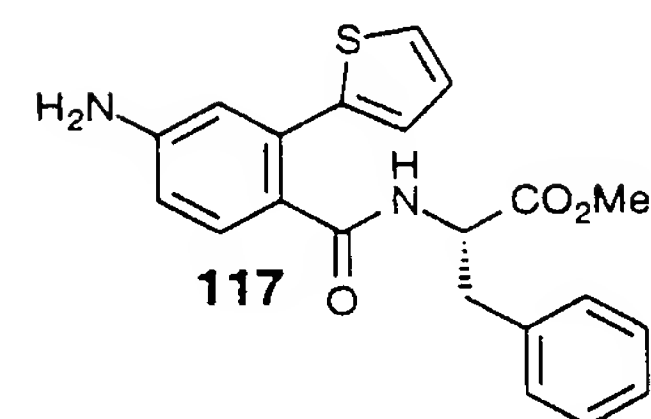
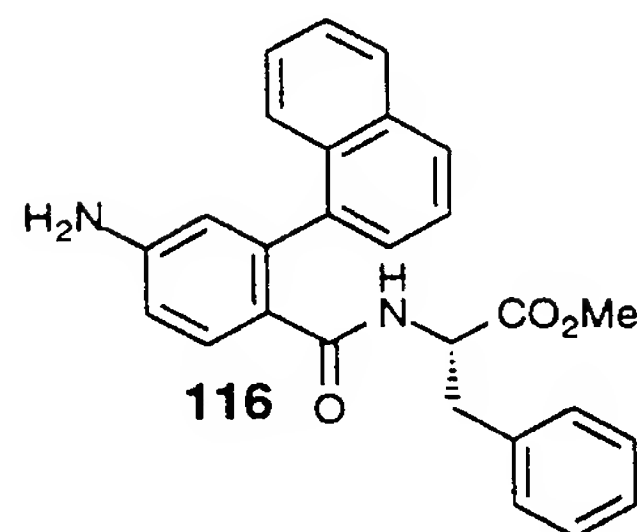
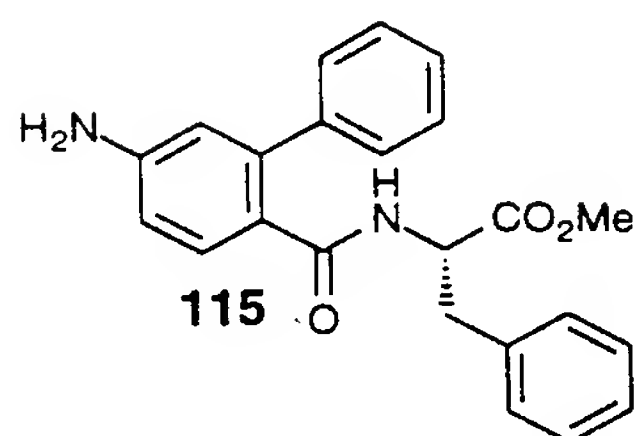
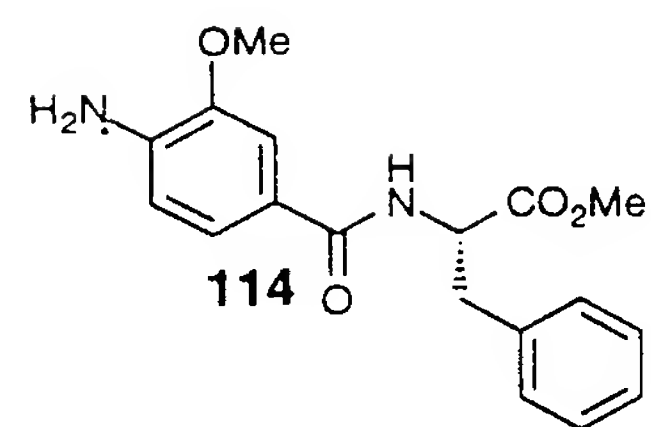
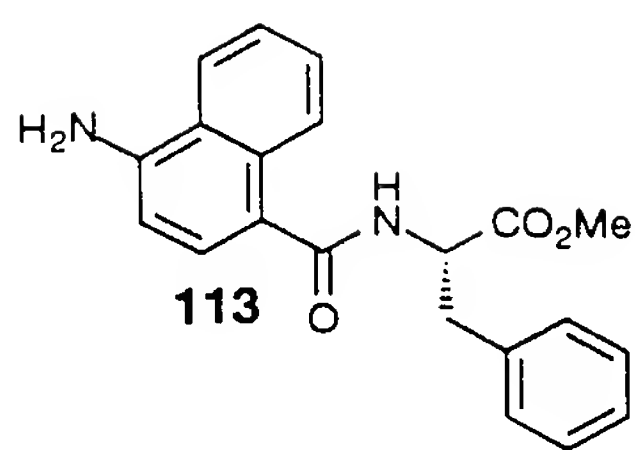
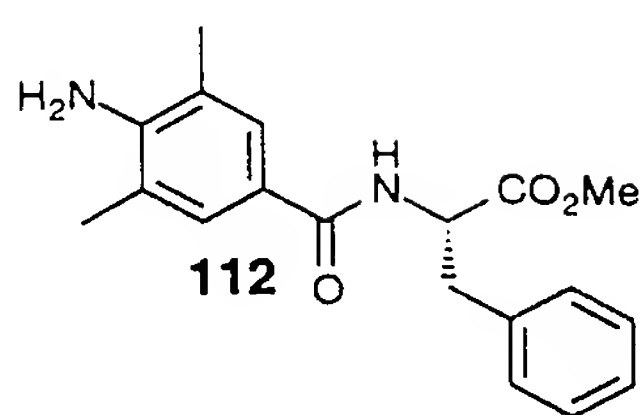


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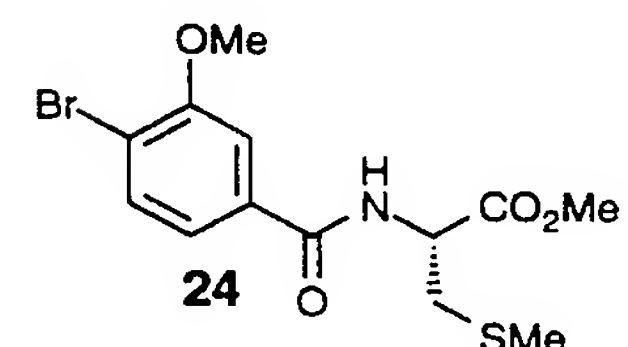
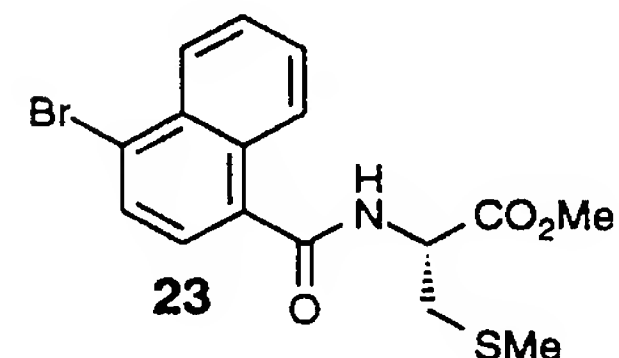
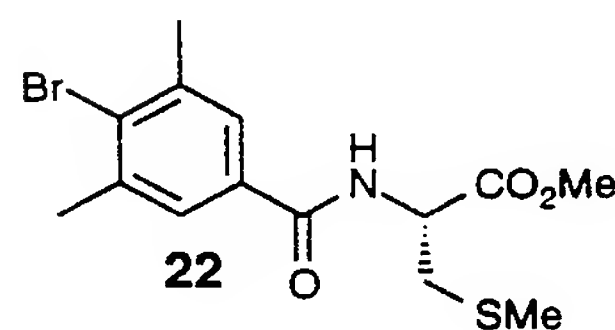
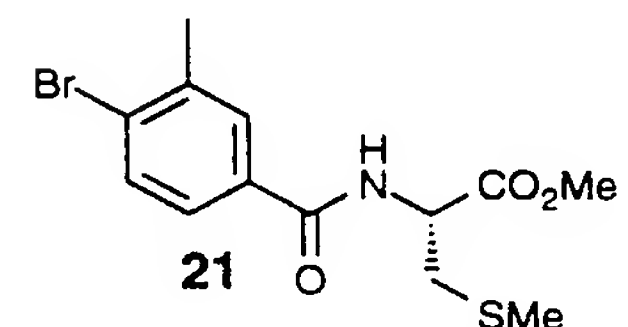
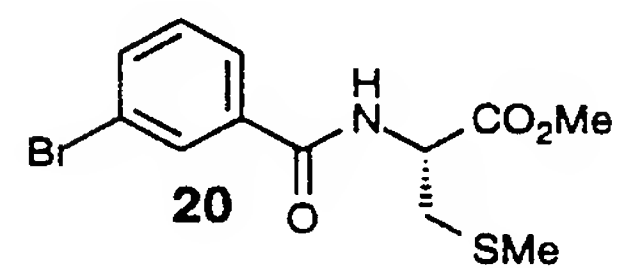
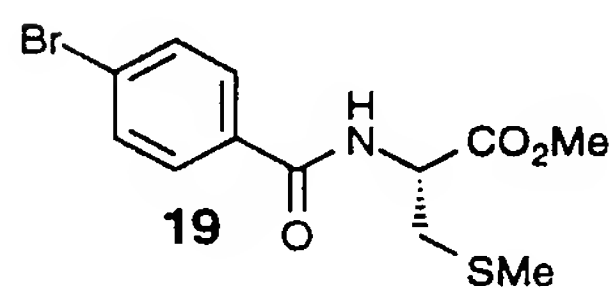
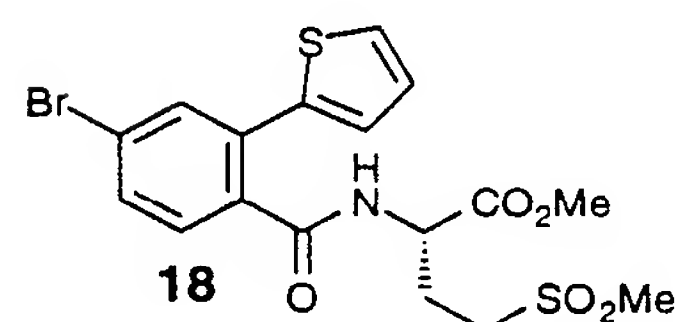
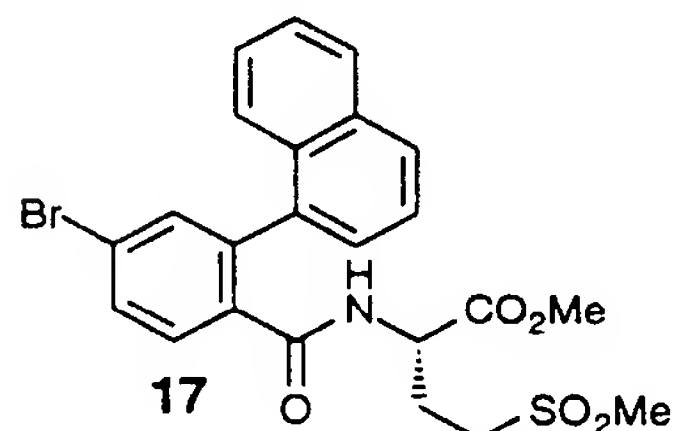
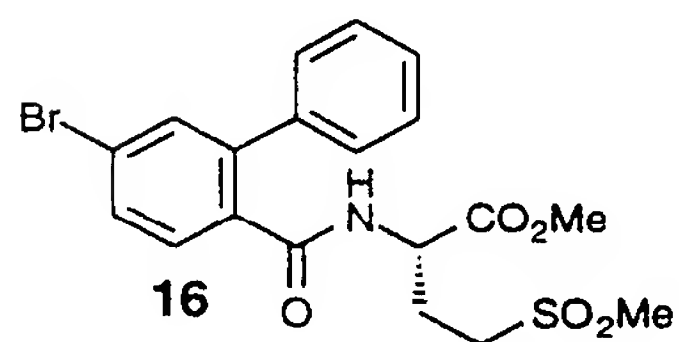
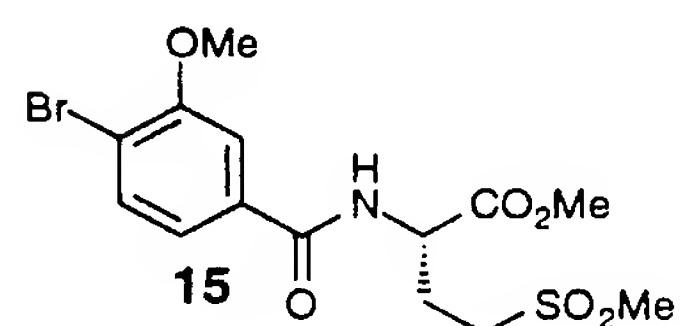
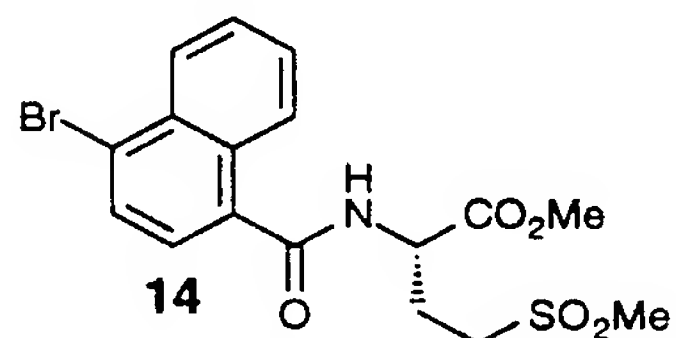
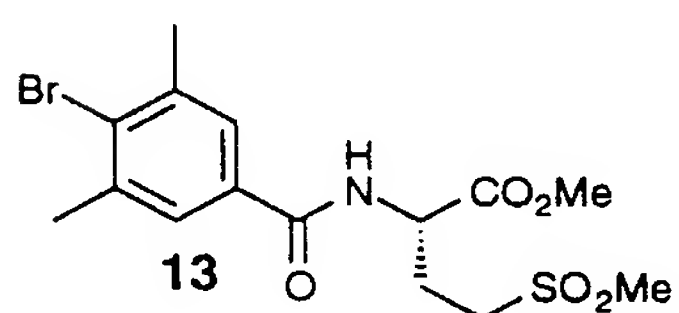
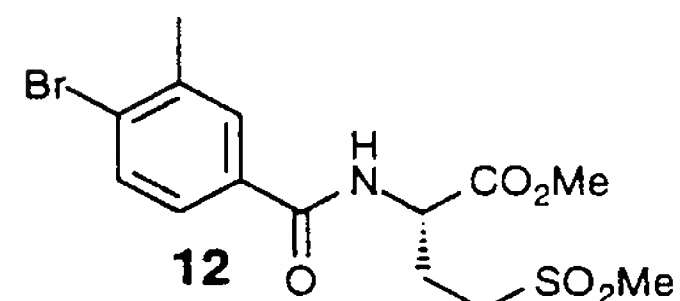
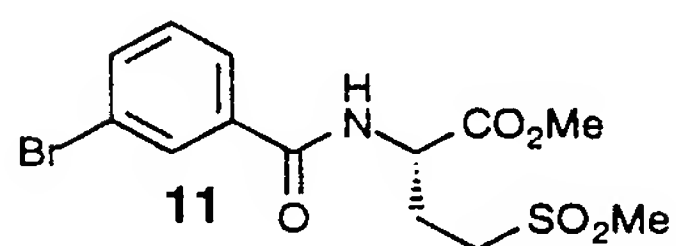
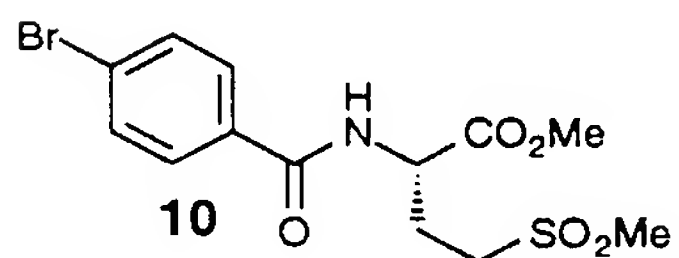
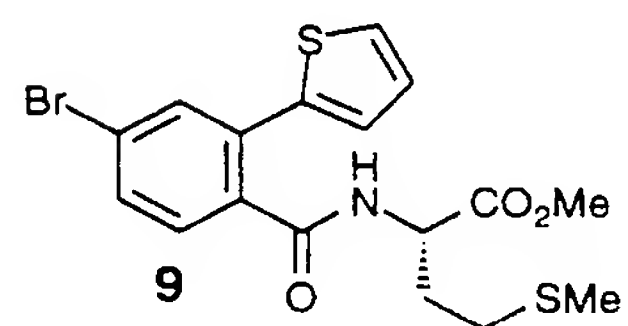
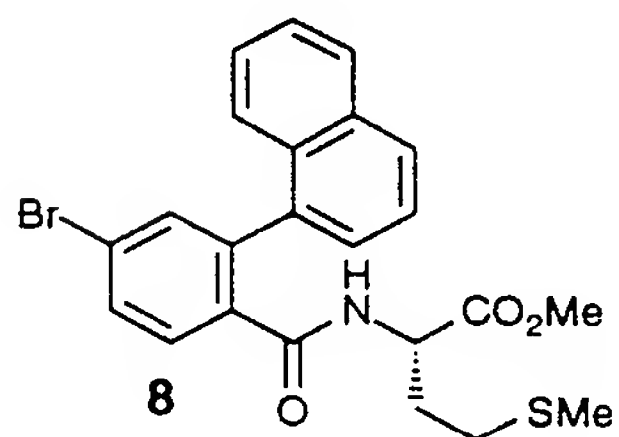
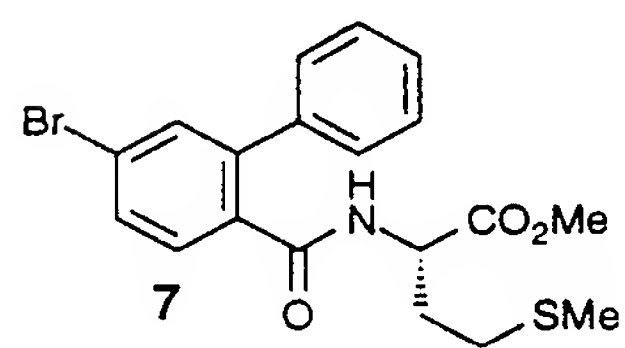
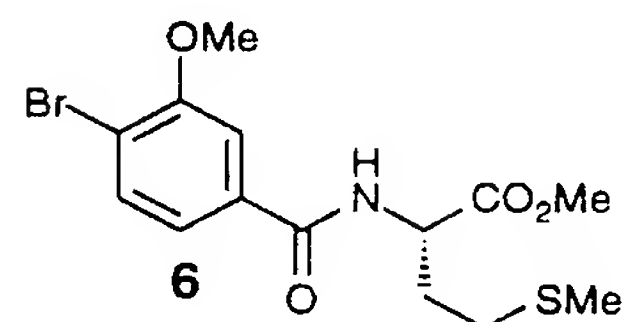
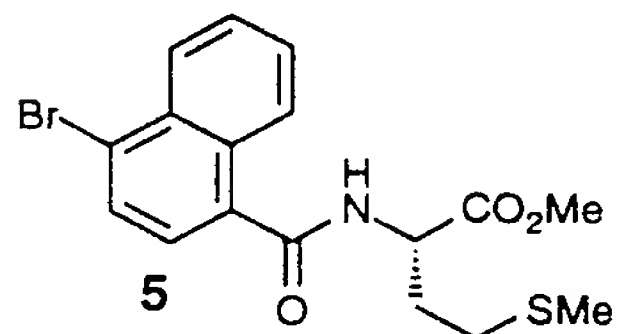
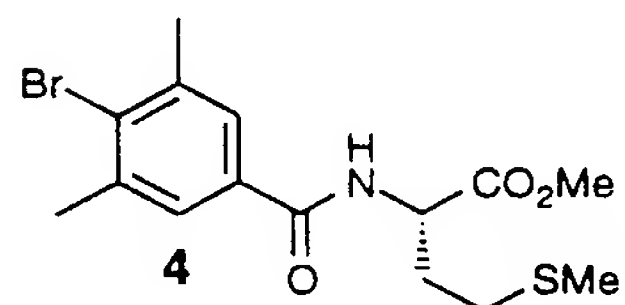
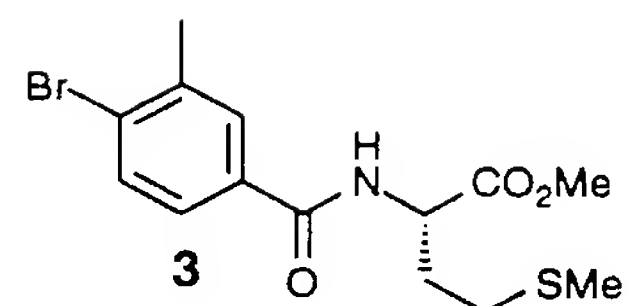
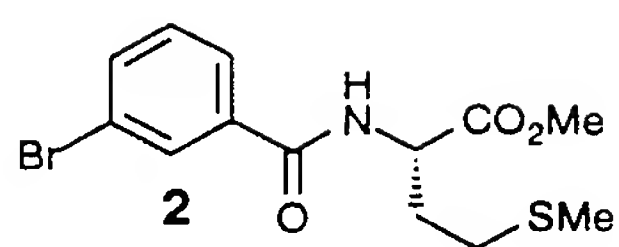
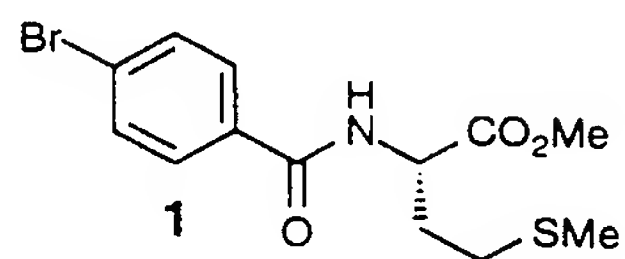
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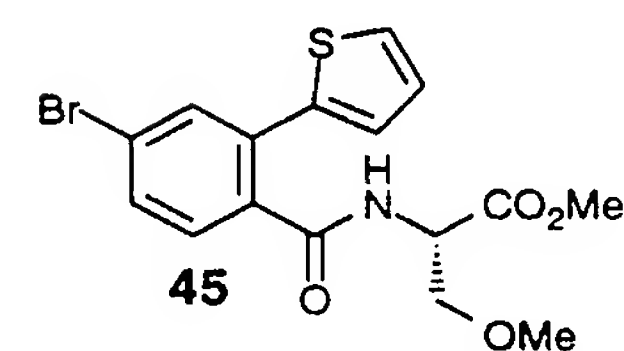
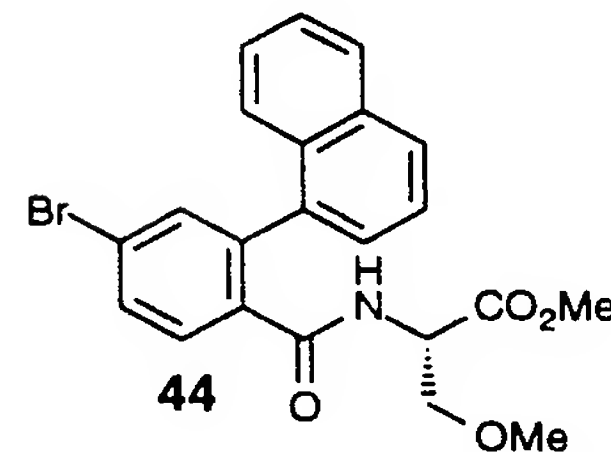
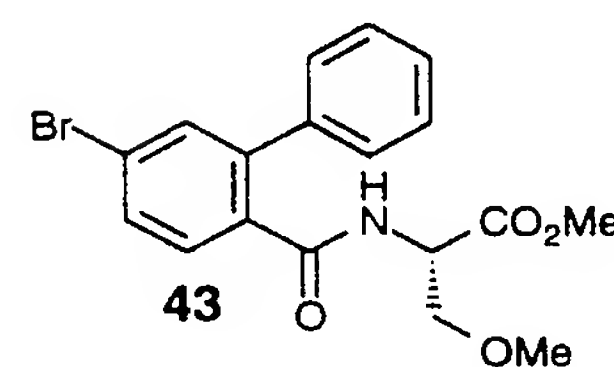
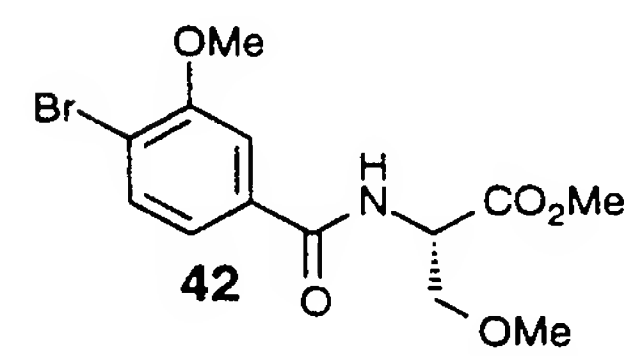
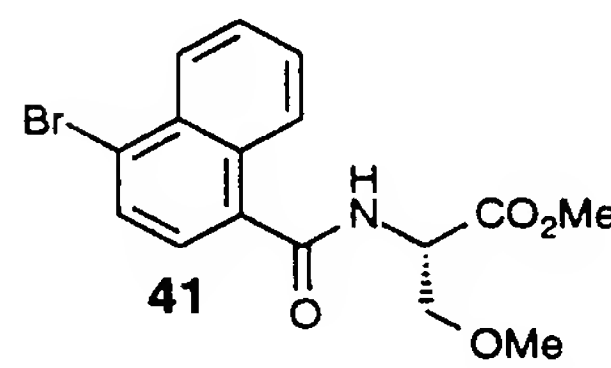
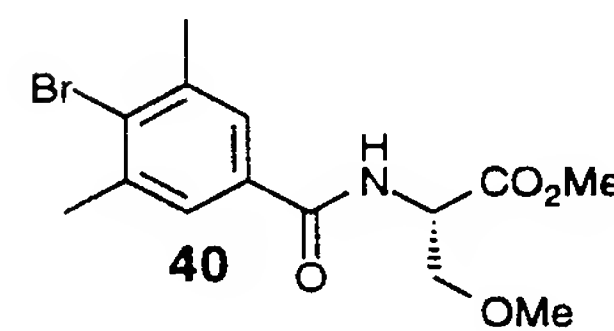
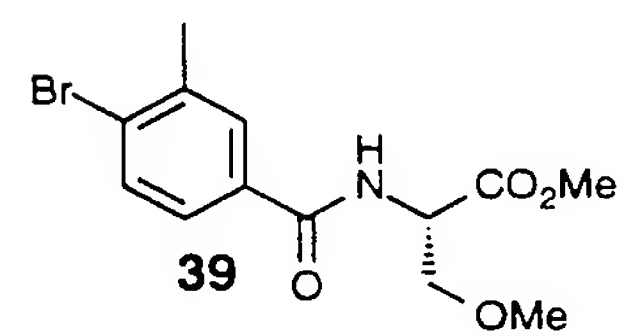
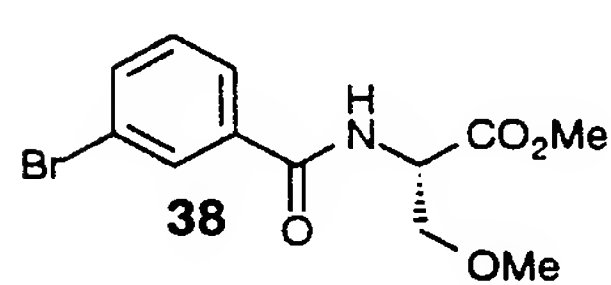
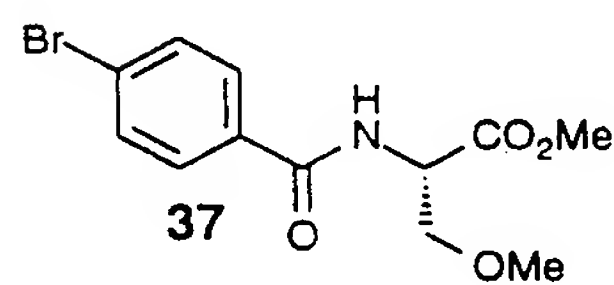
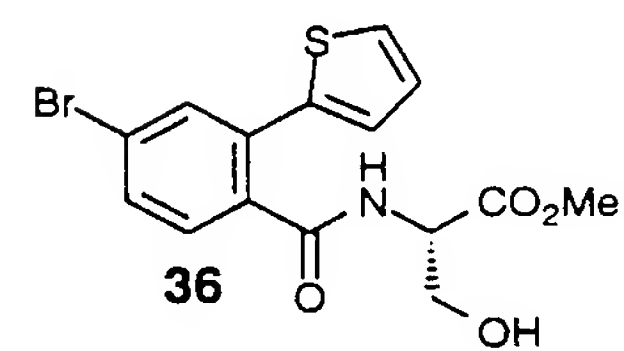
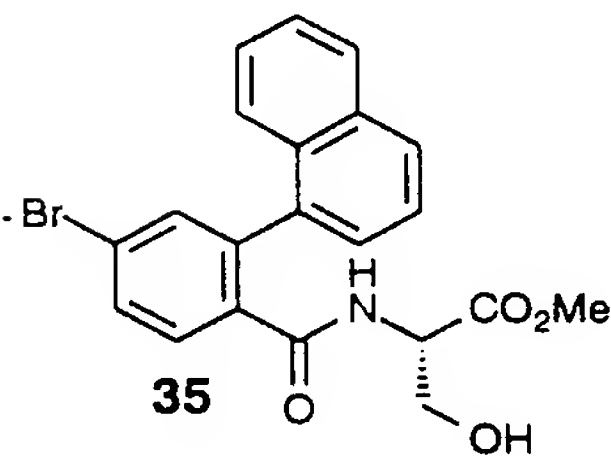
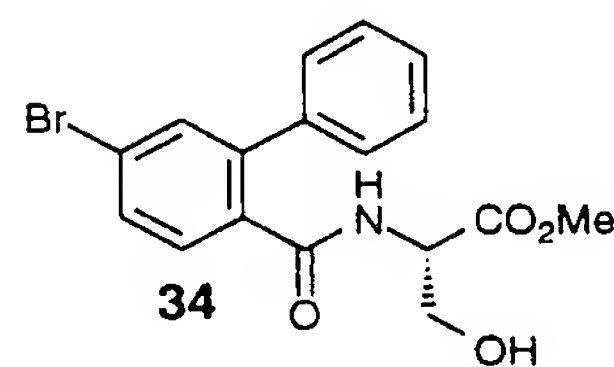
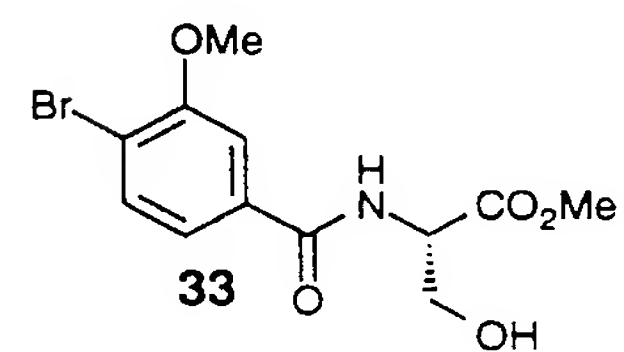
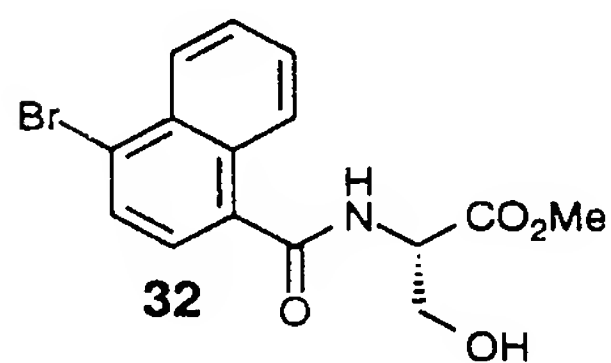
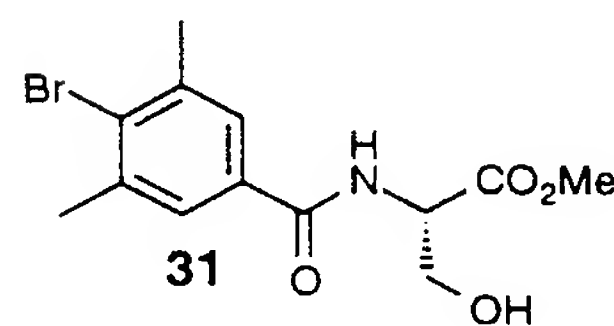
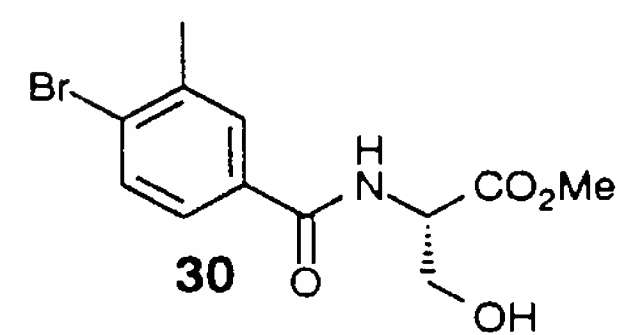
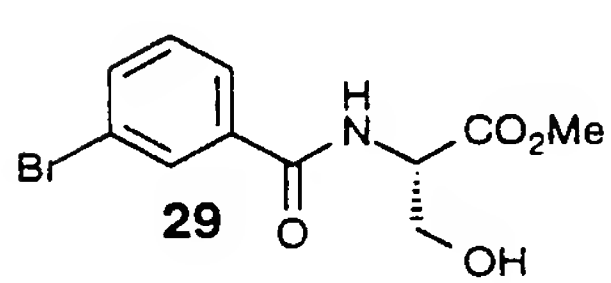
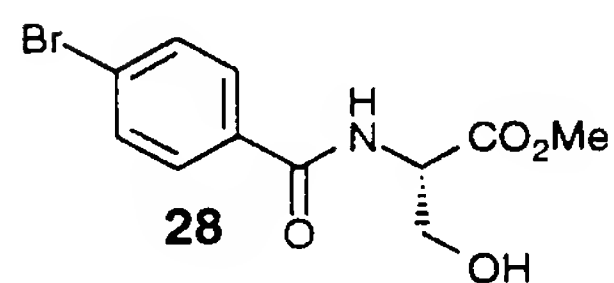
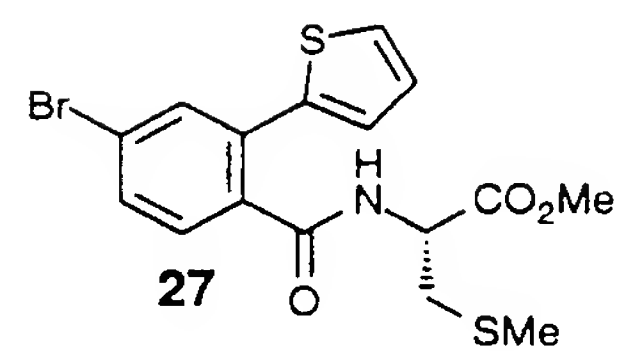
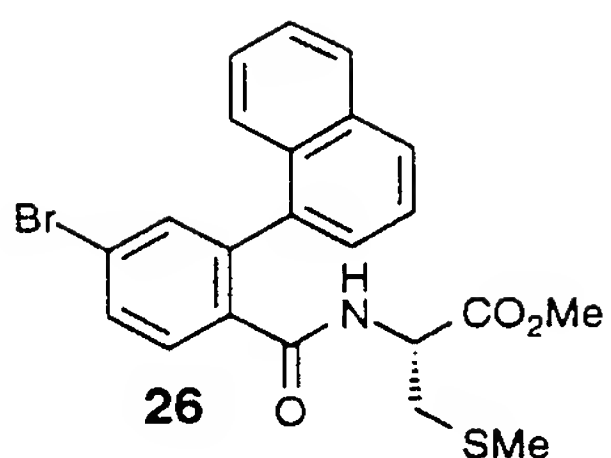
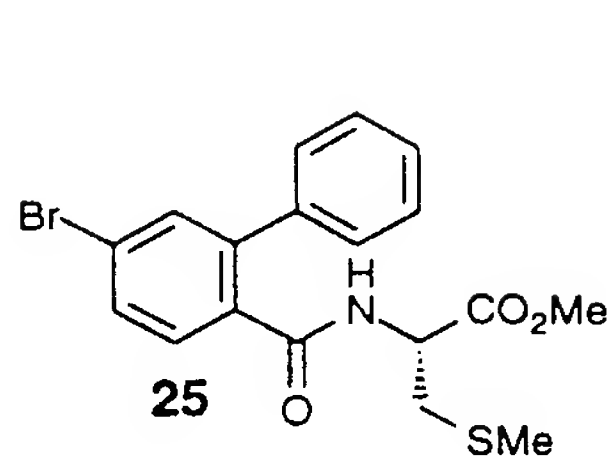


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2565 Table 11. Bromides of the type B-Br

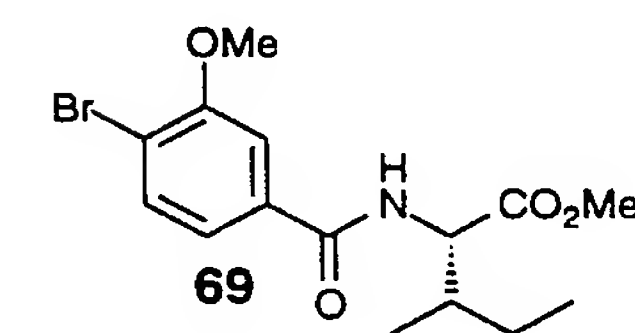
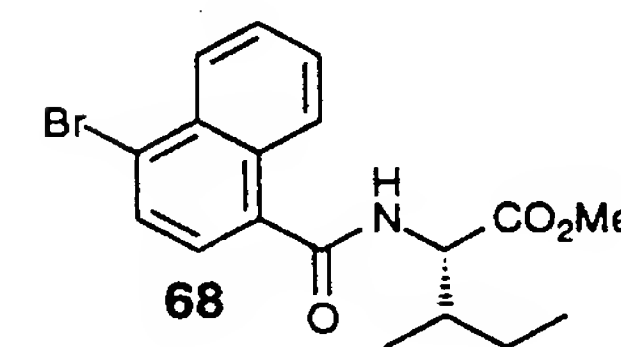
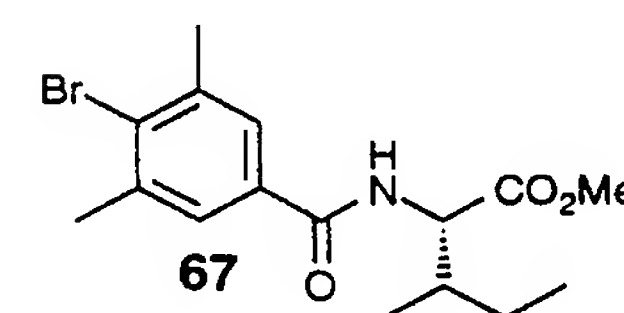
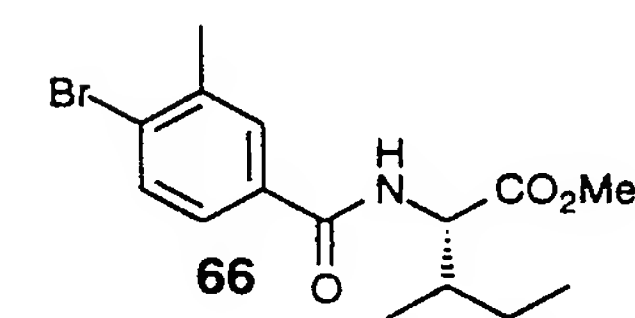
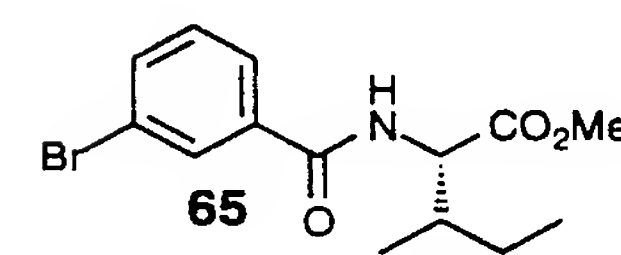
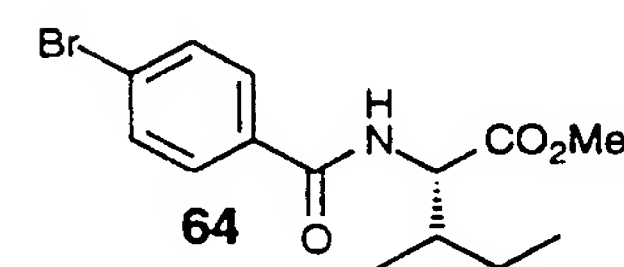
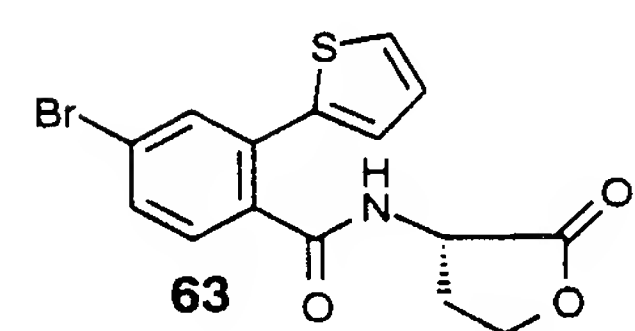
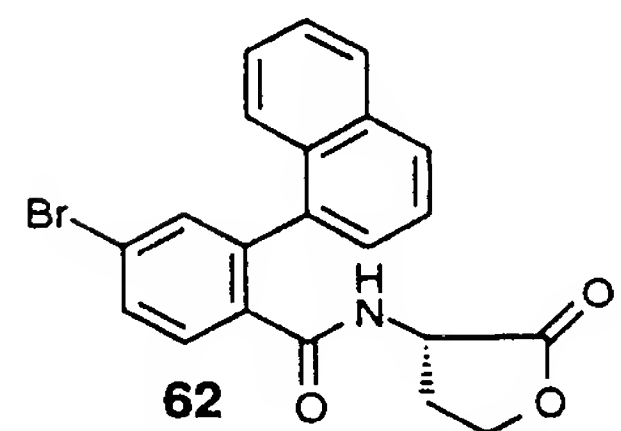
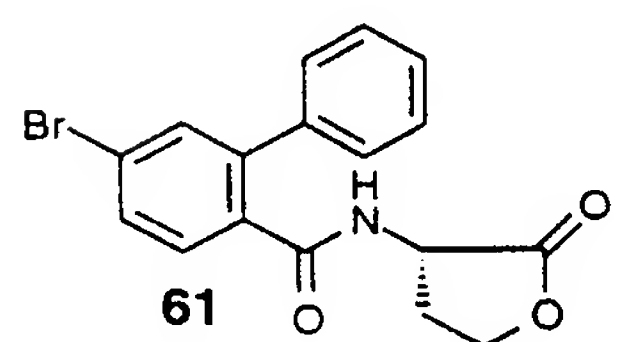
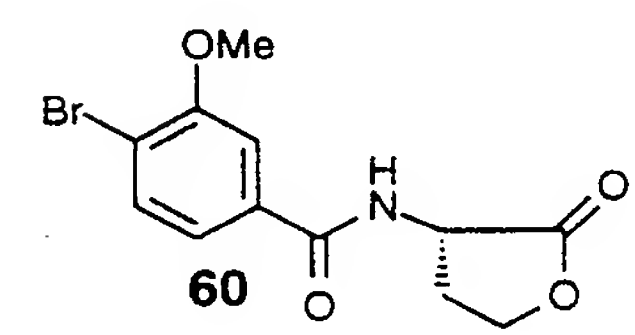
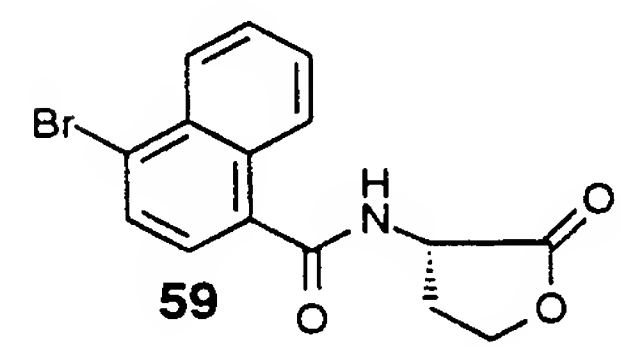
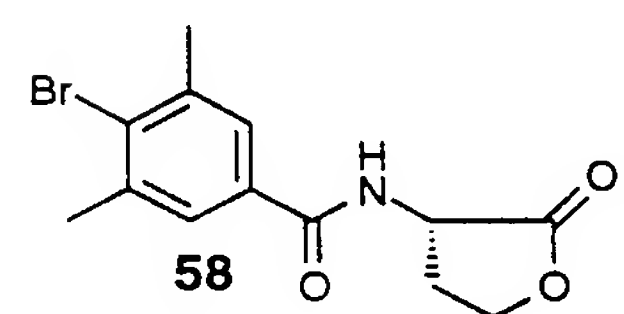
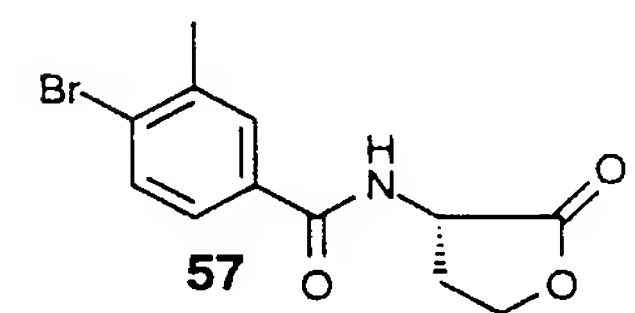
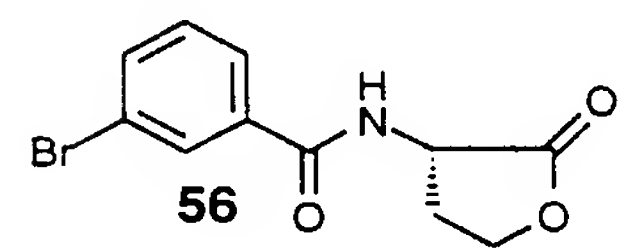
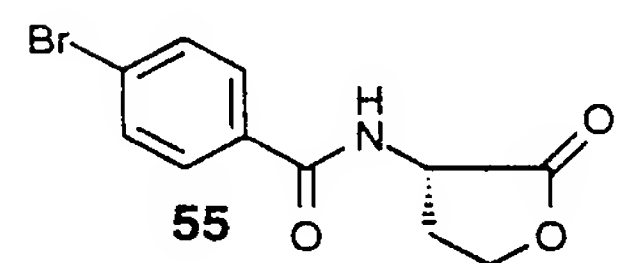
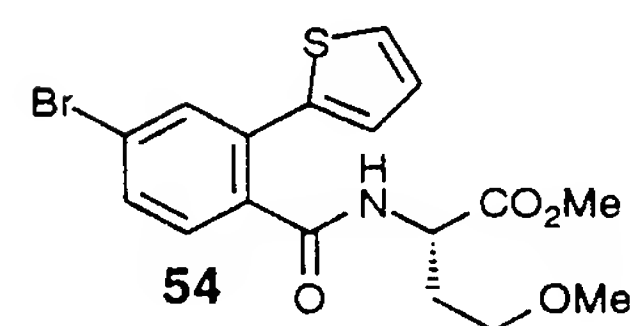
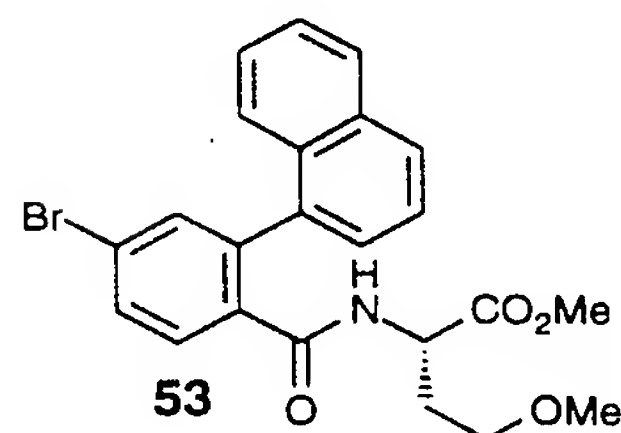
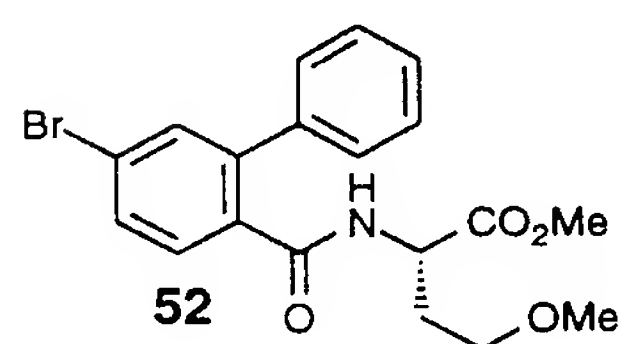
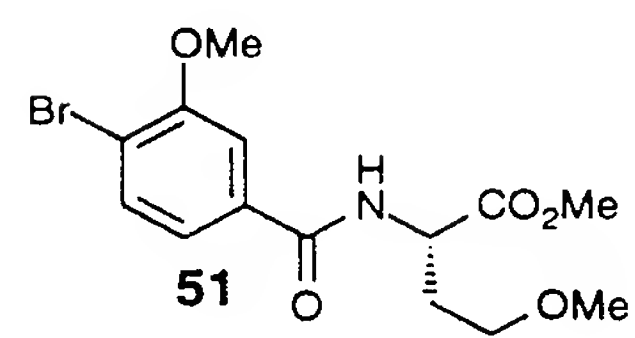
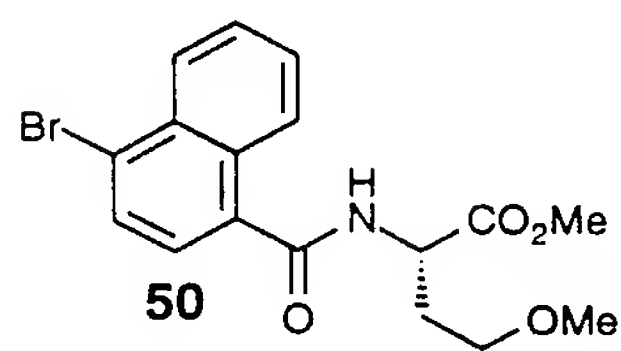
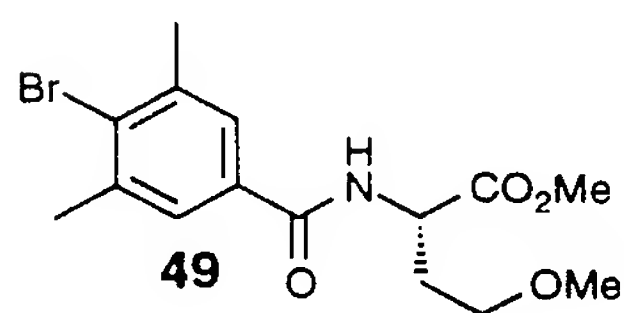
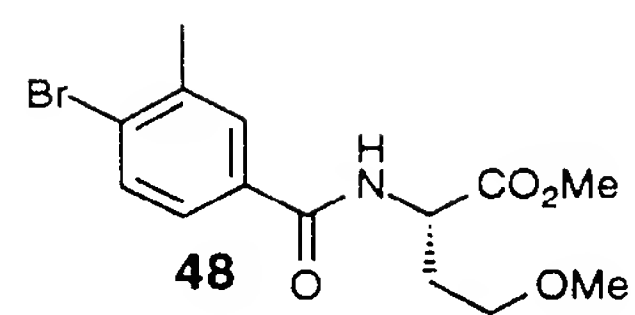
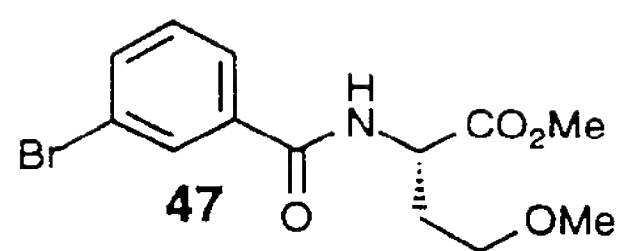
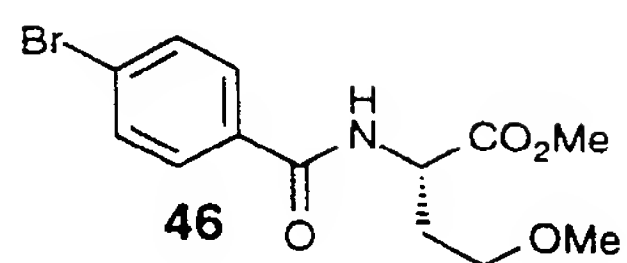


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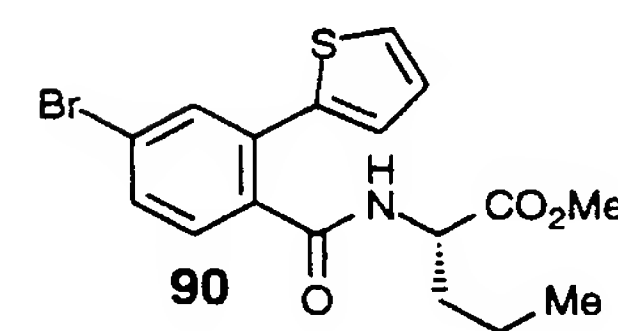
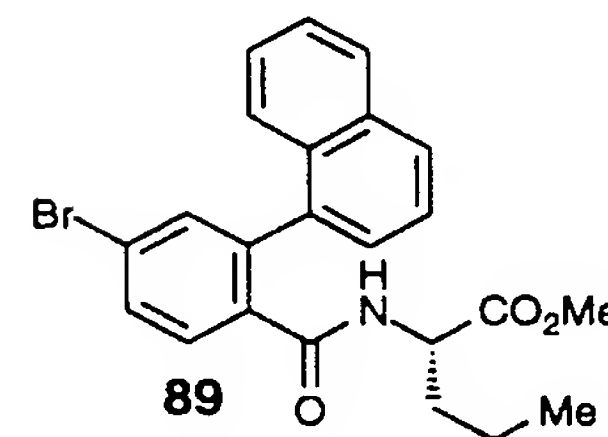
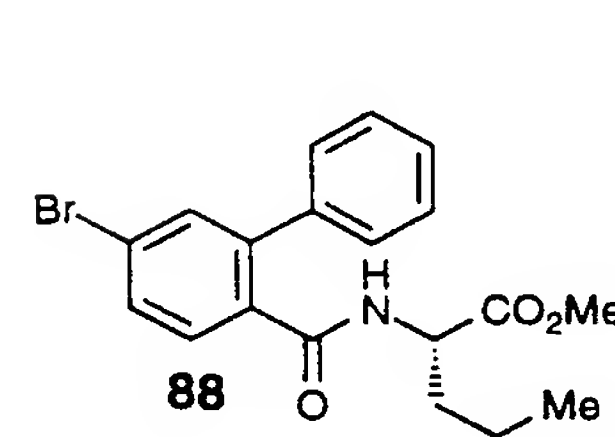
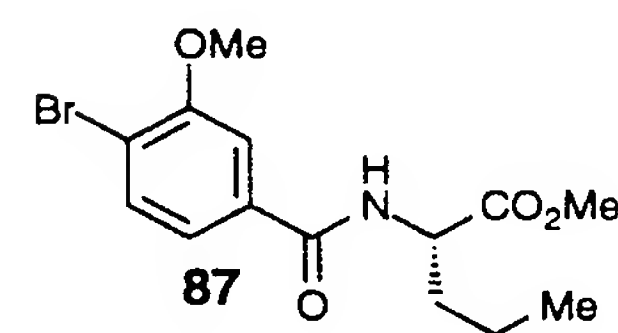
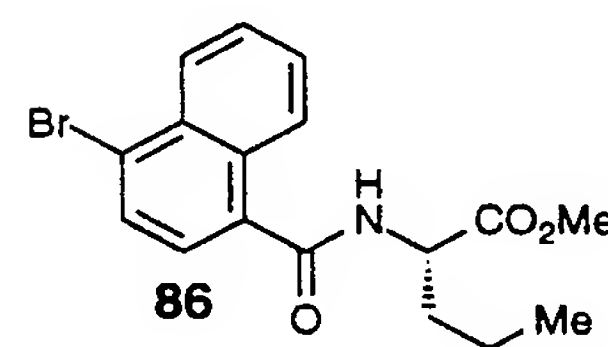
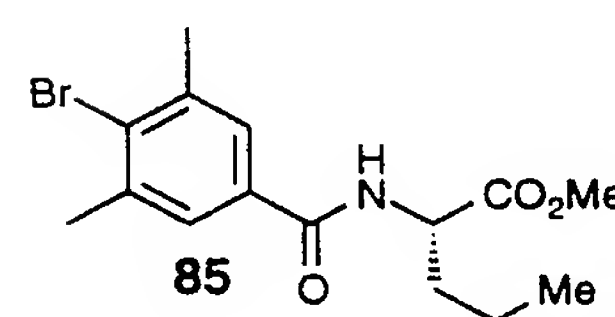
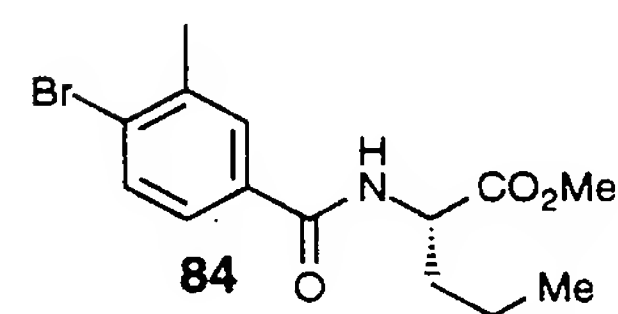
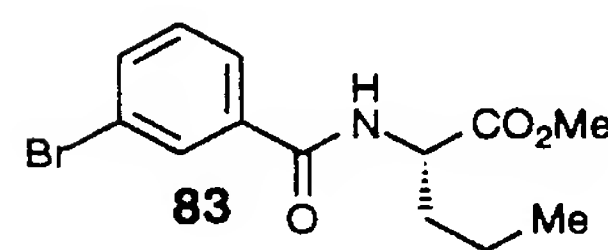
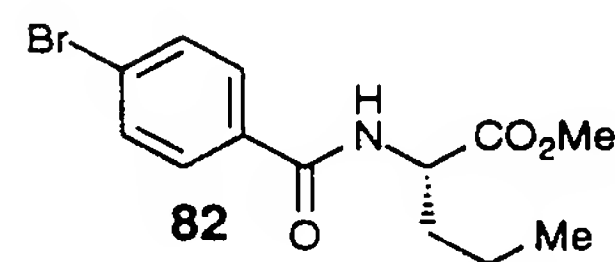
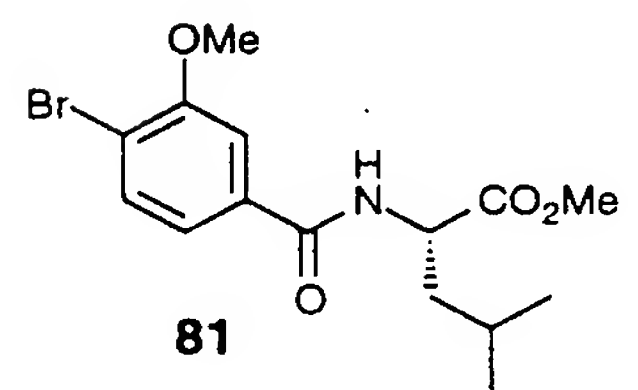
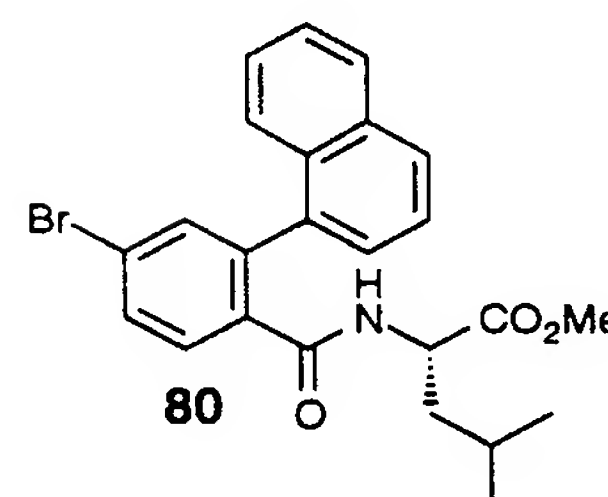
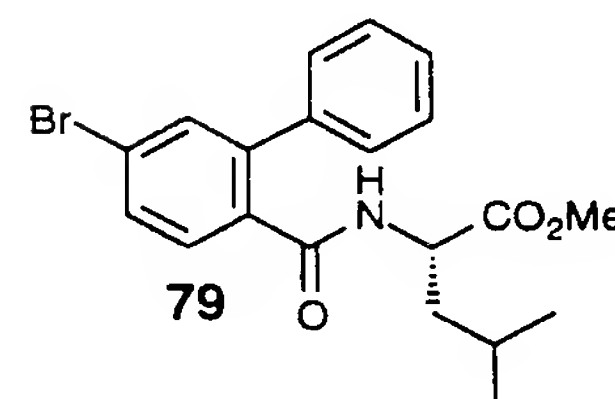
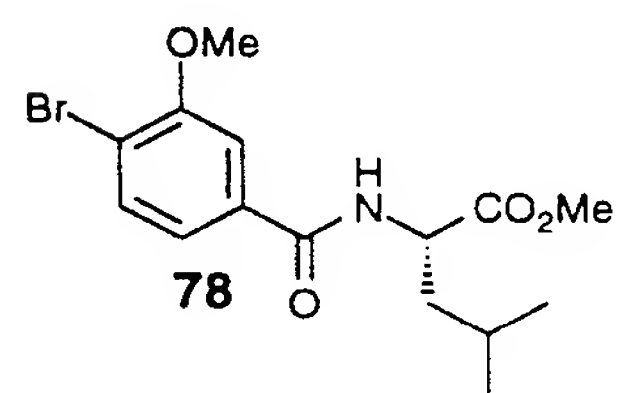
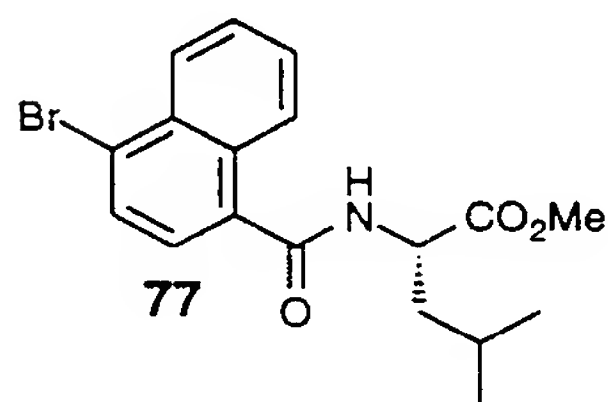
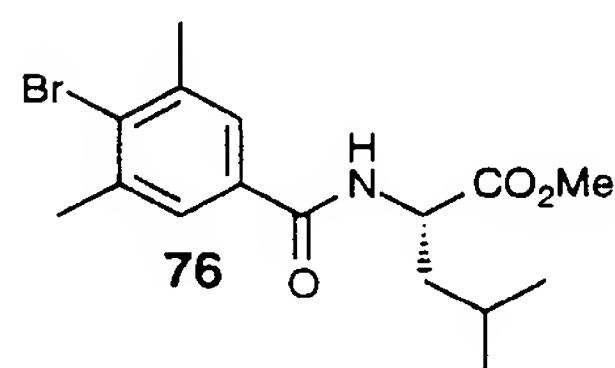
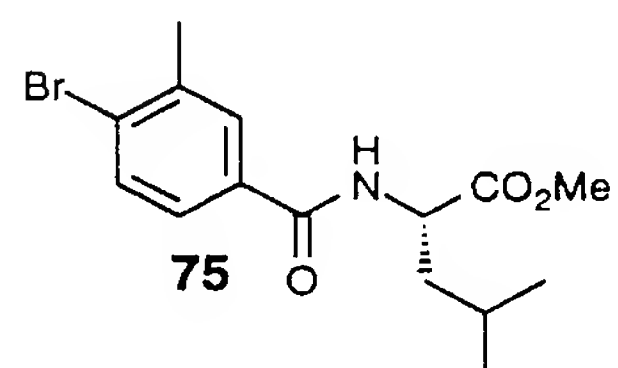
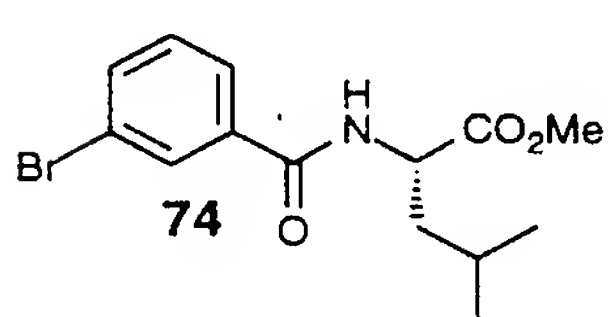
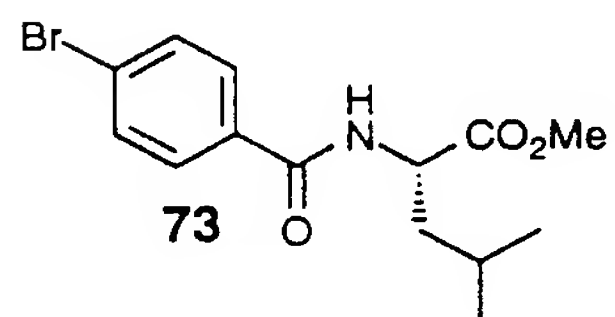
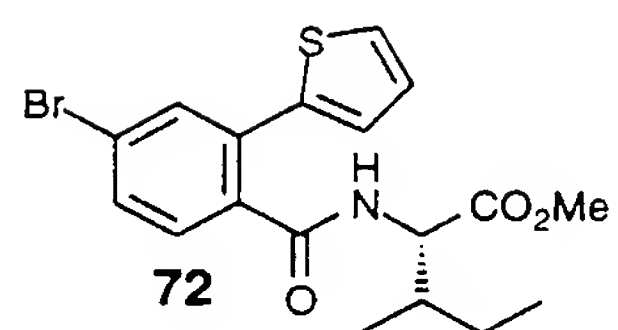
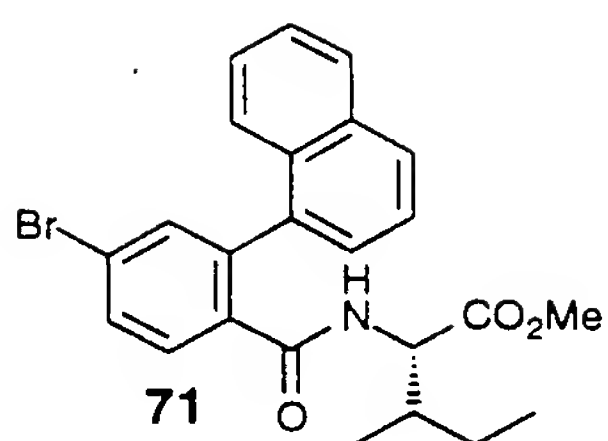
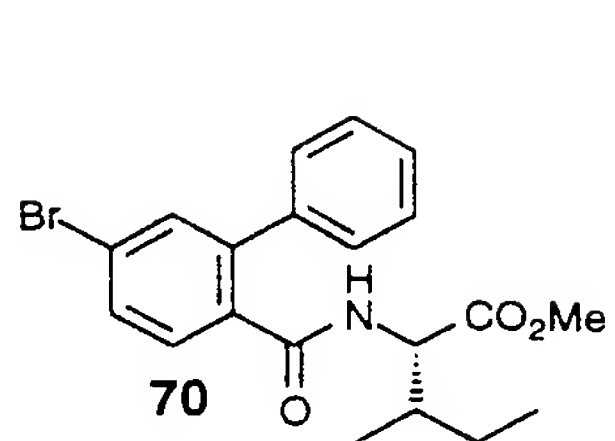


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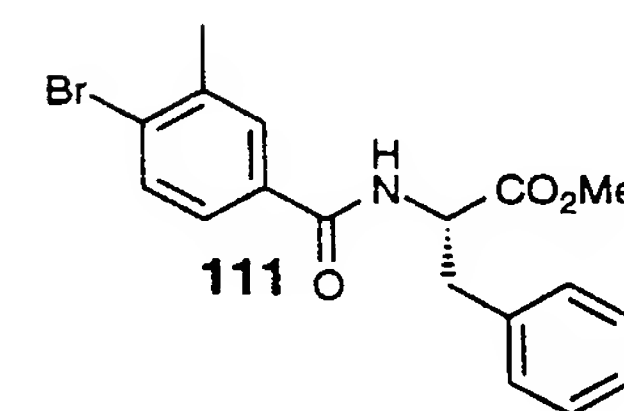
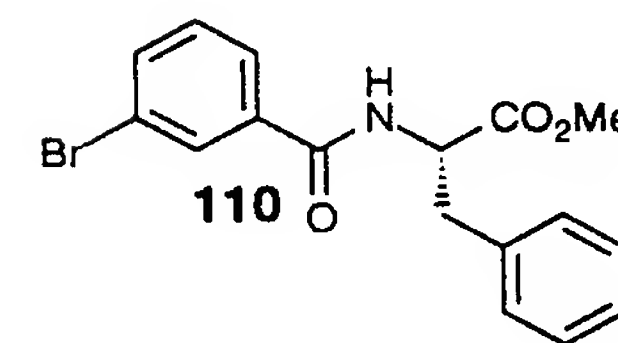
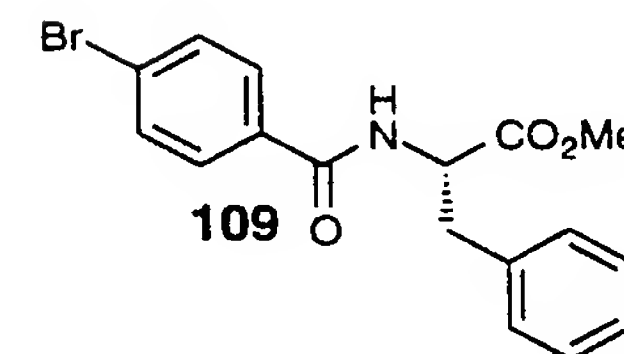
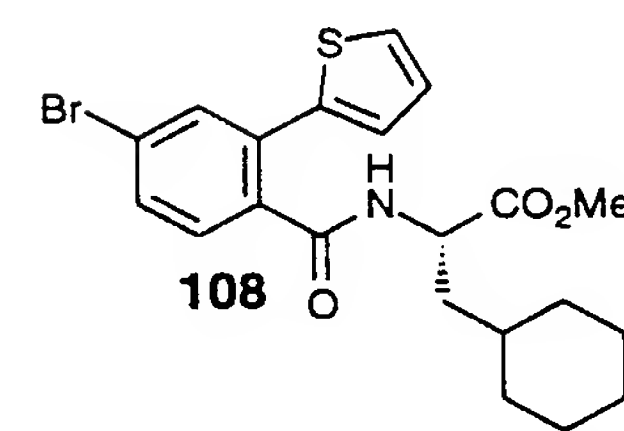
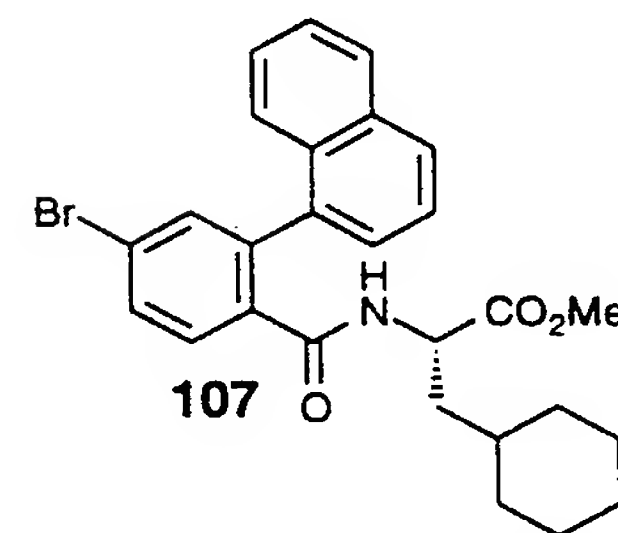
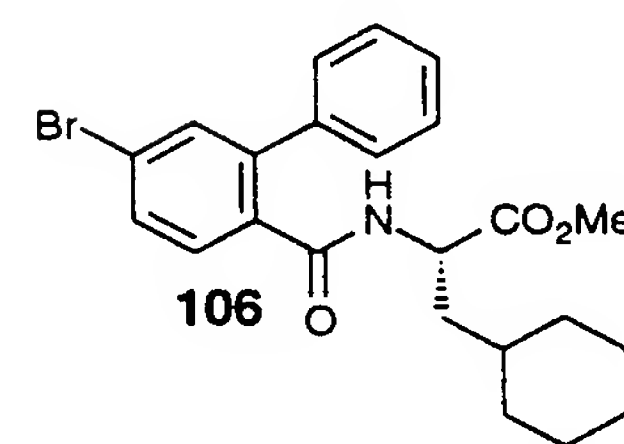
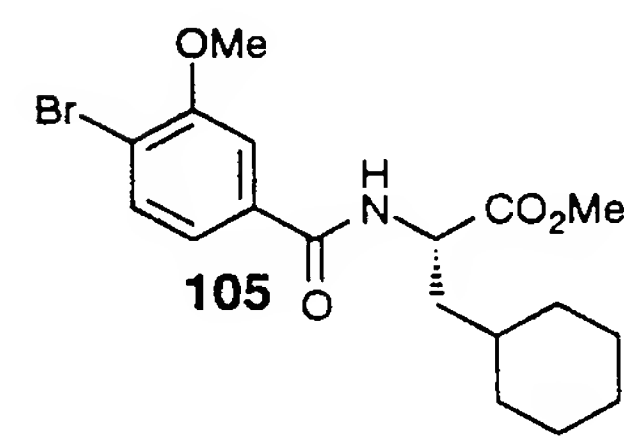
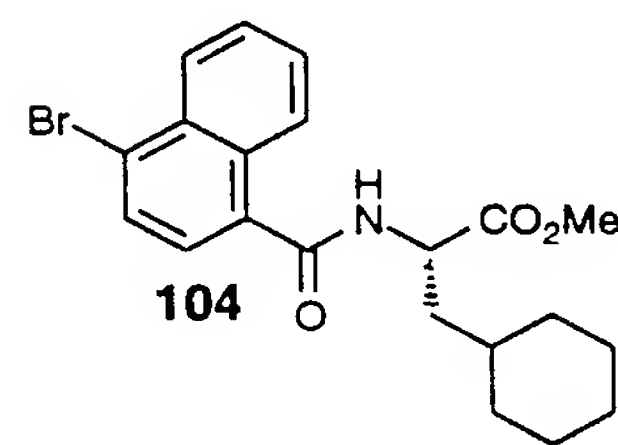
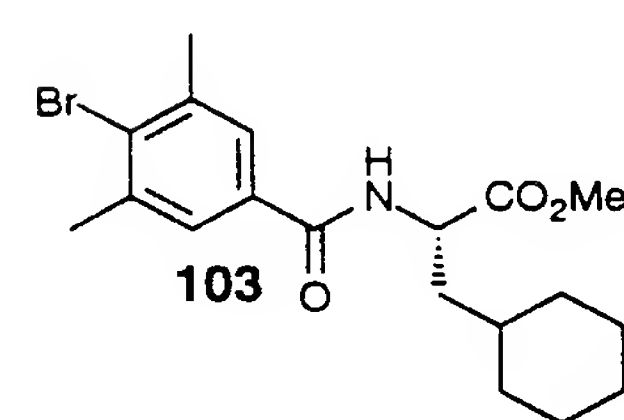
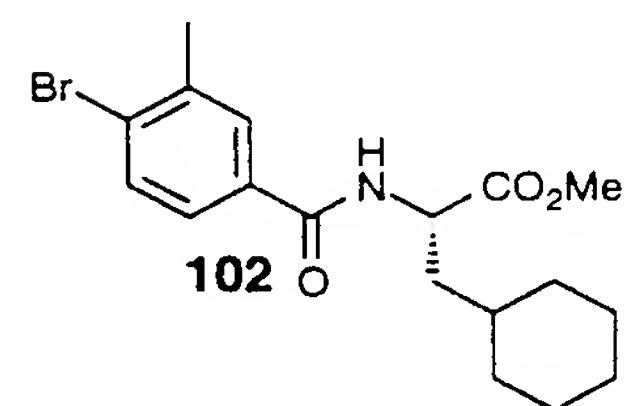
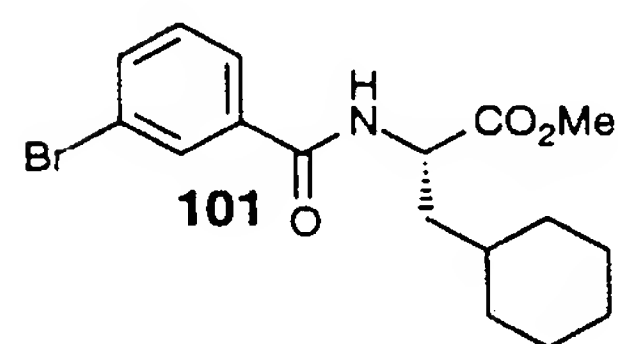
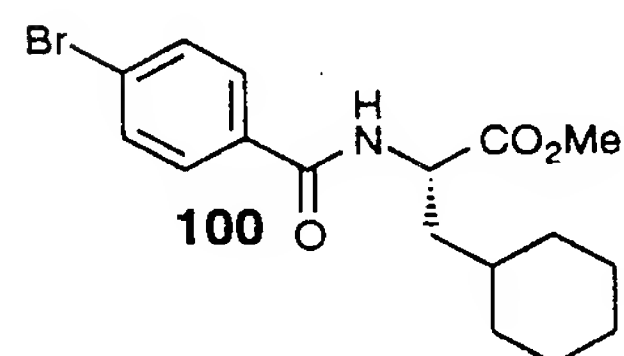
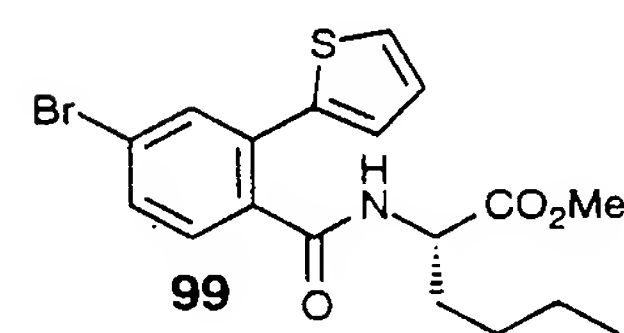
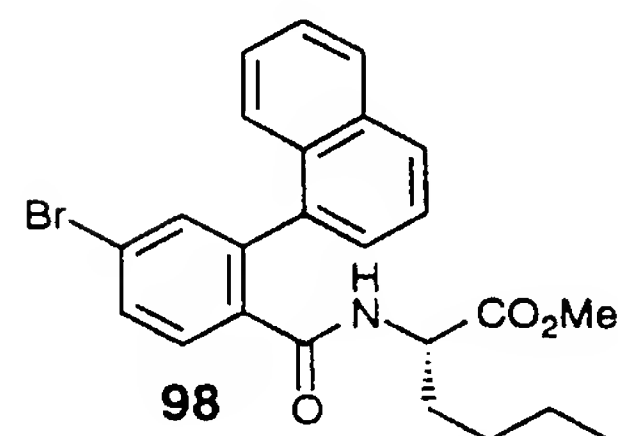
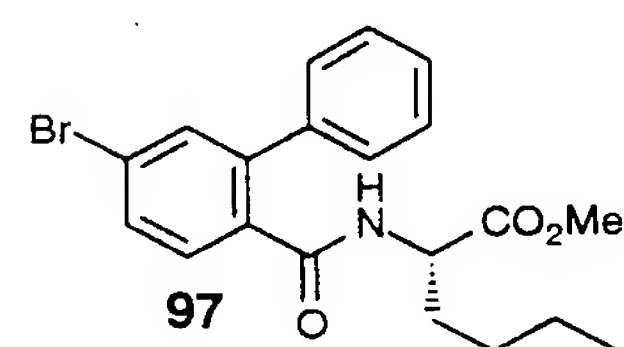
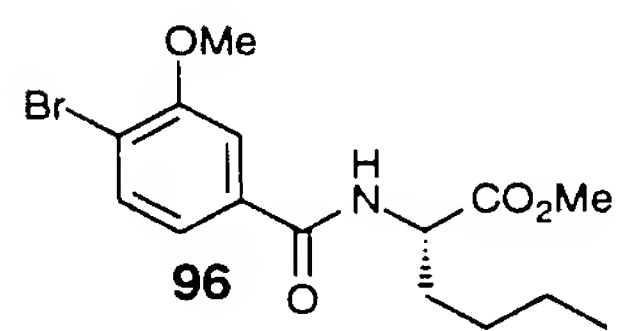
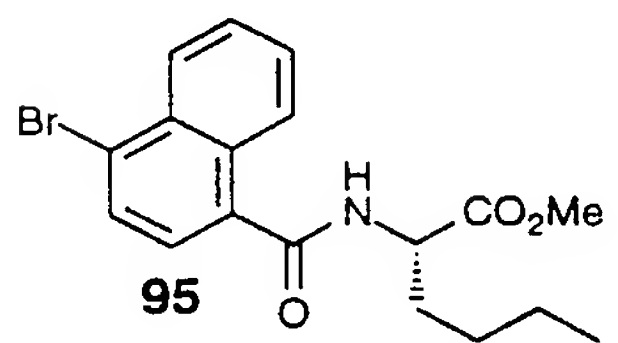
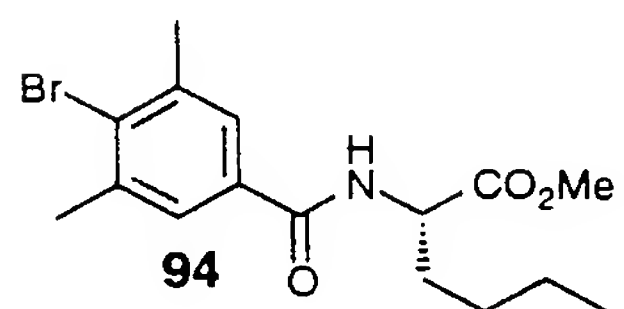
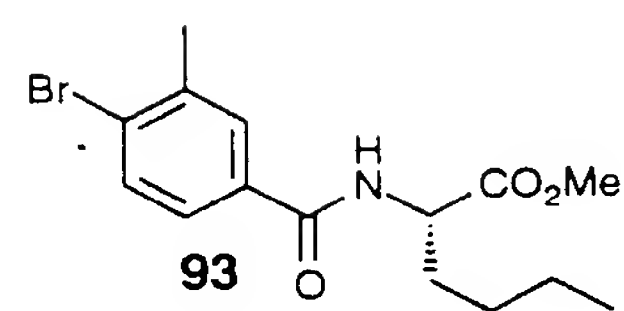
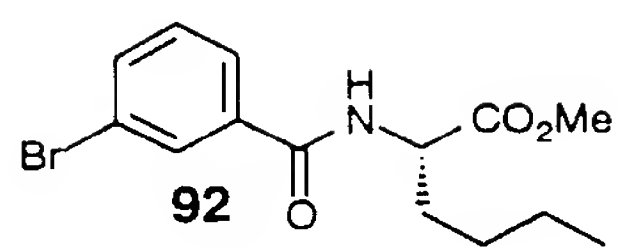
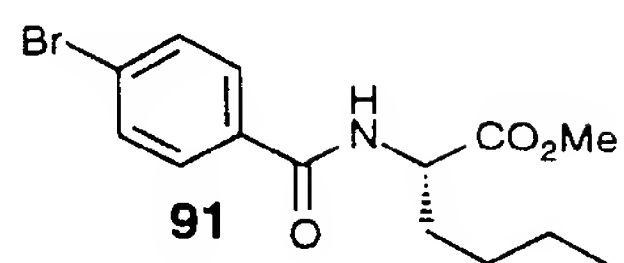




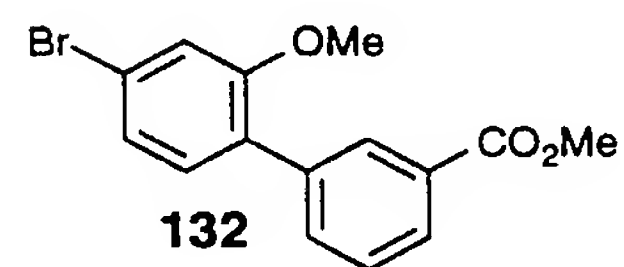
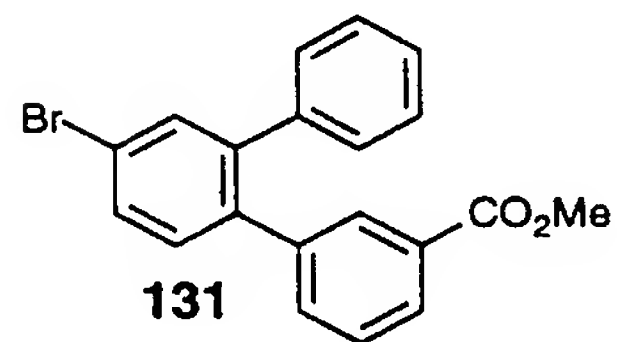
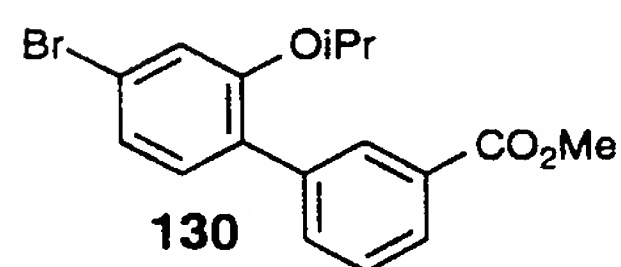
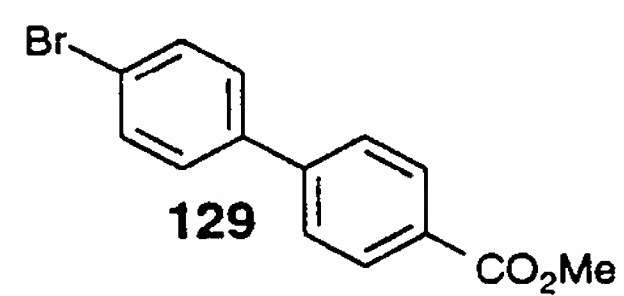
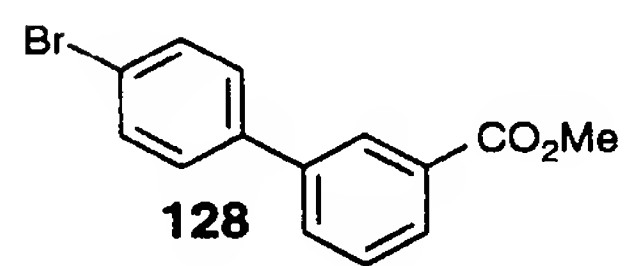
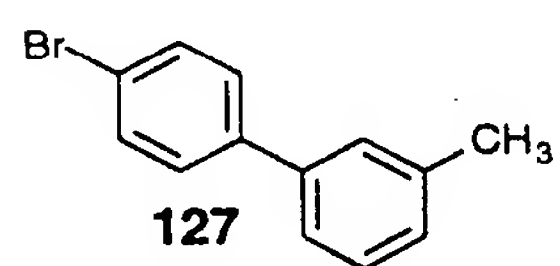
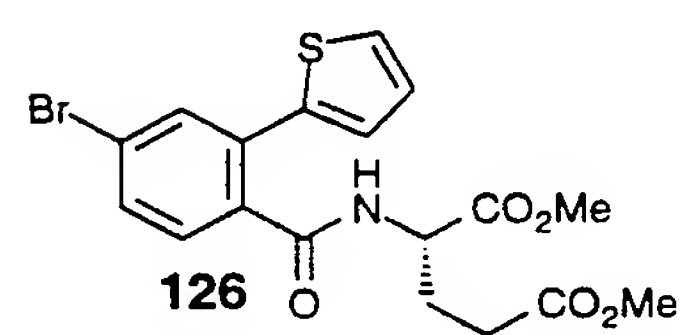
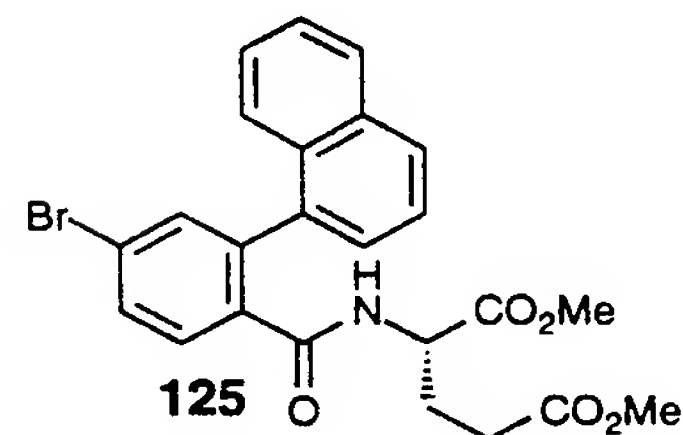
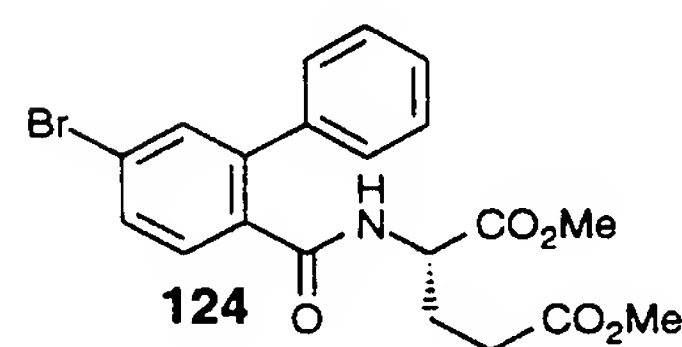
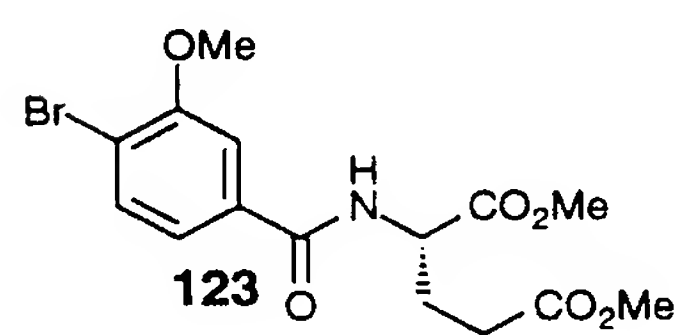
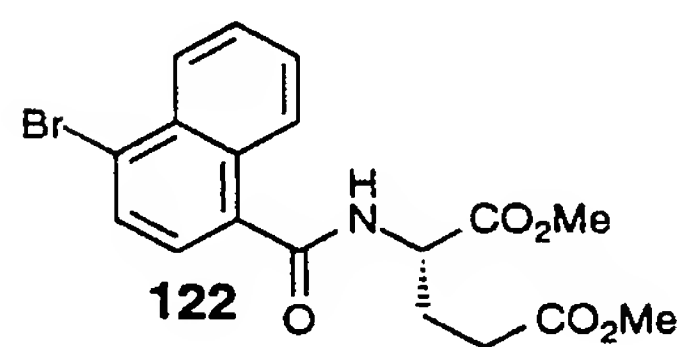
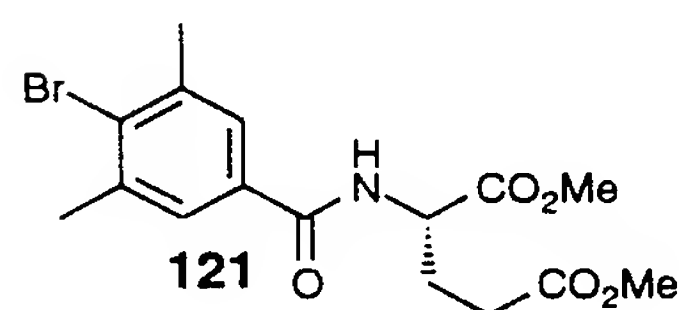
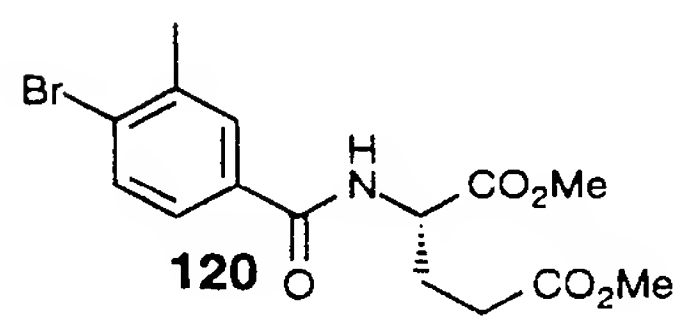
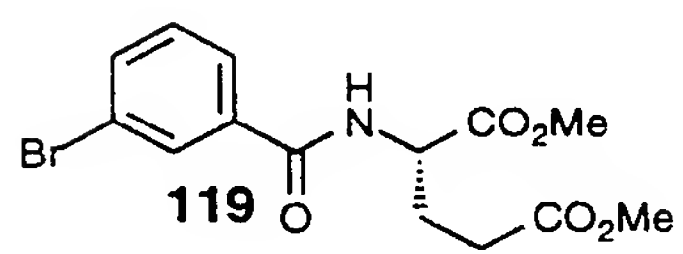
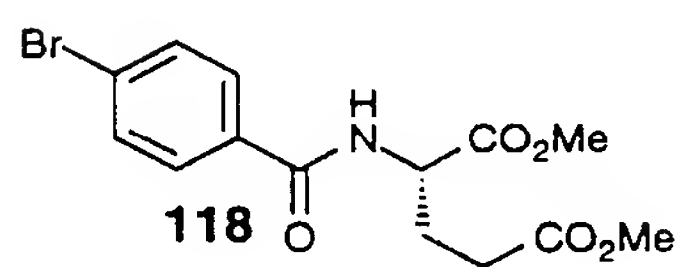
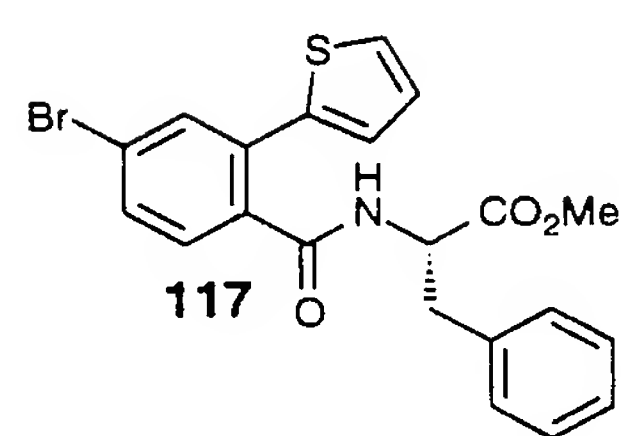
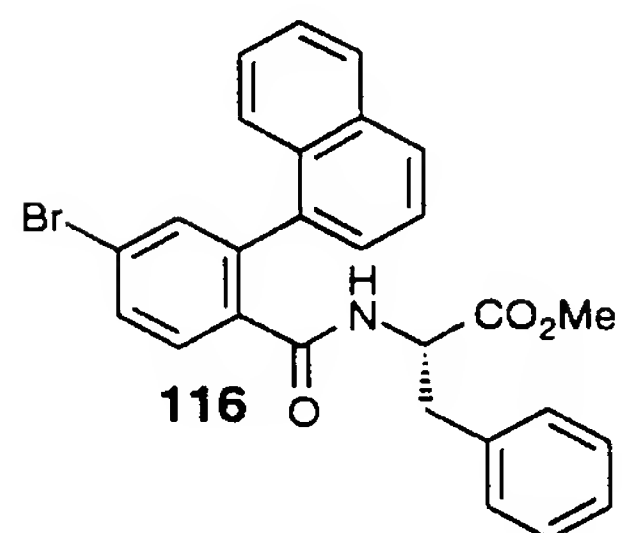
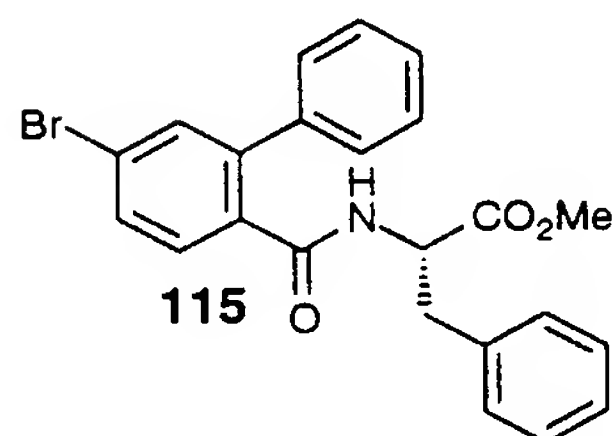
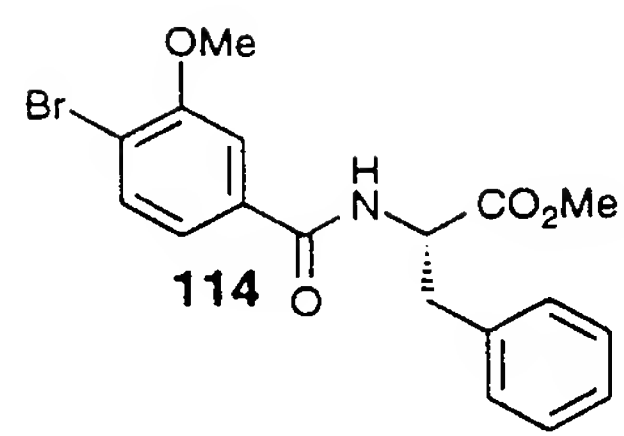
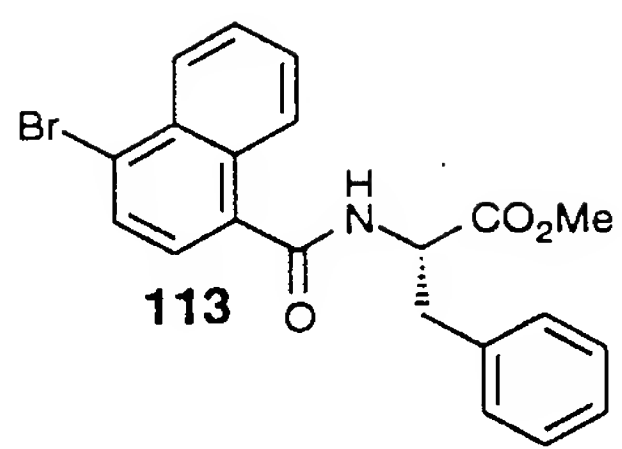
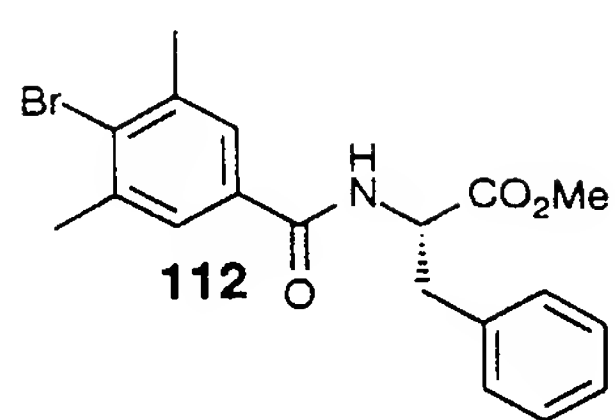


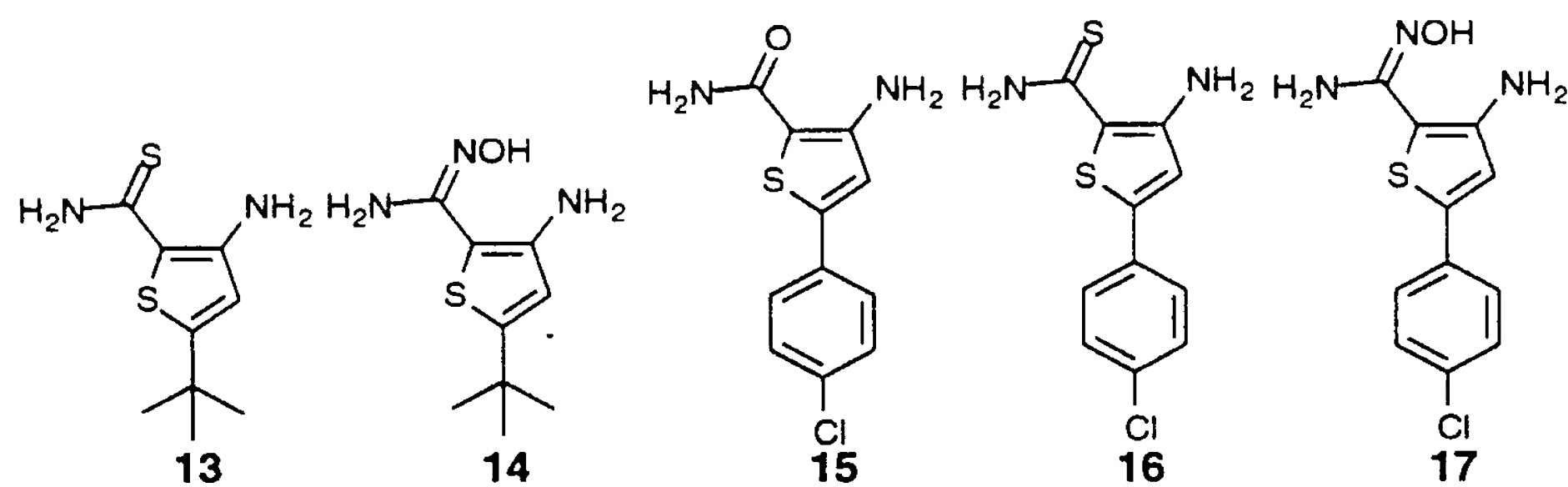
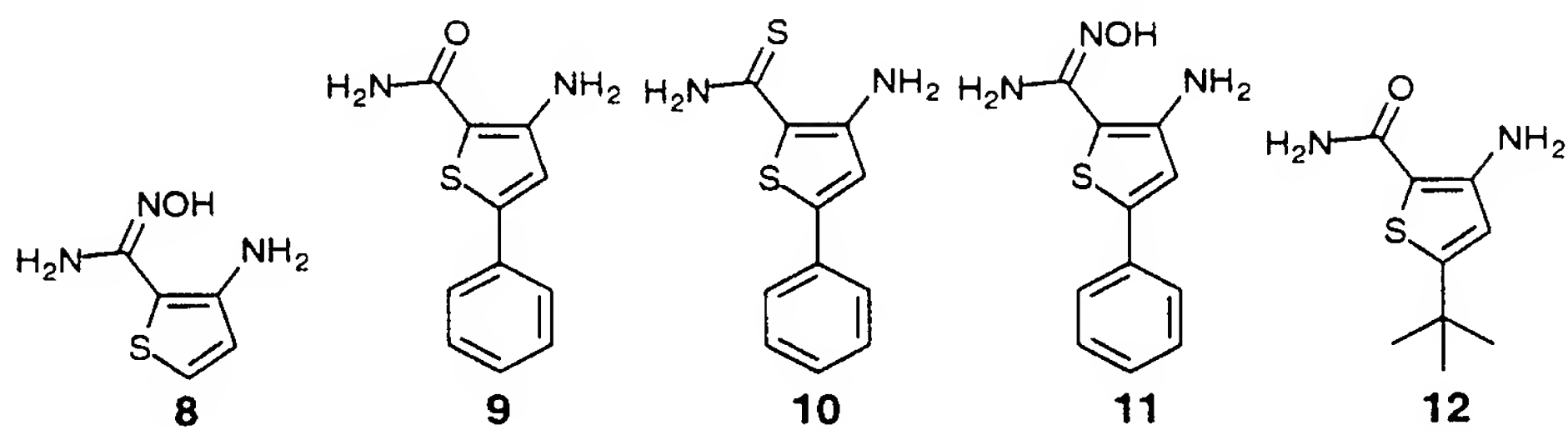
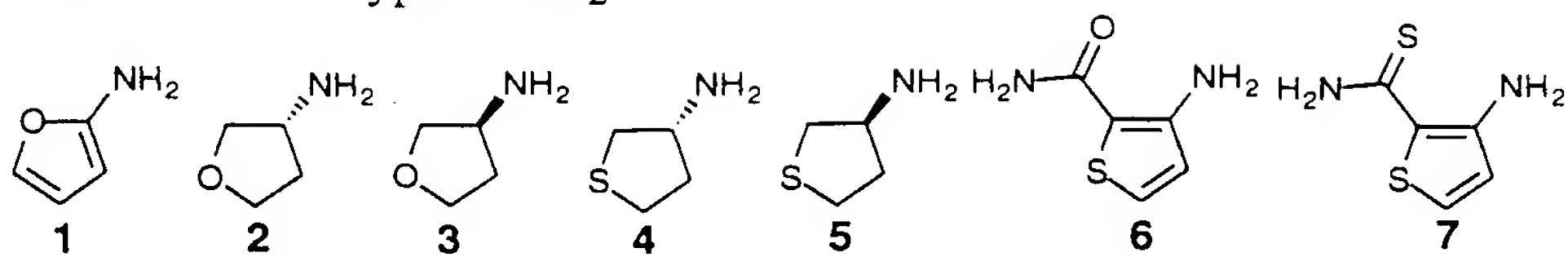
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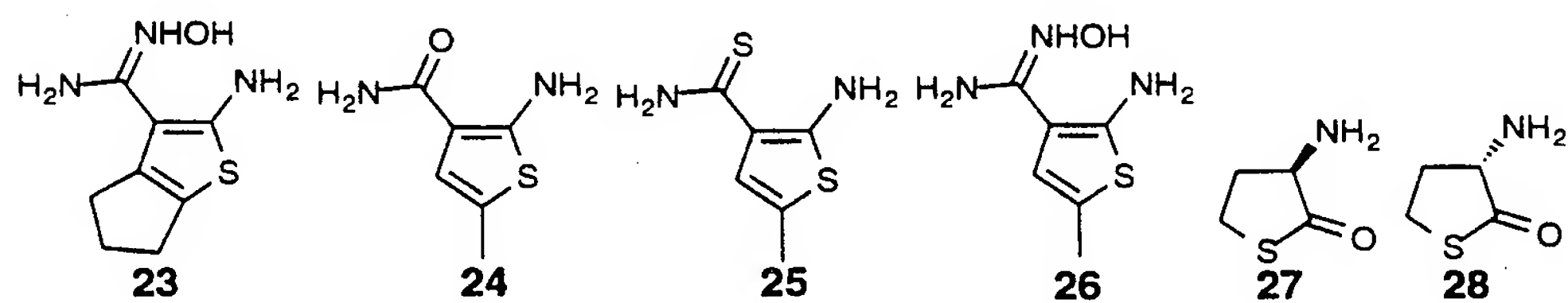
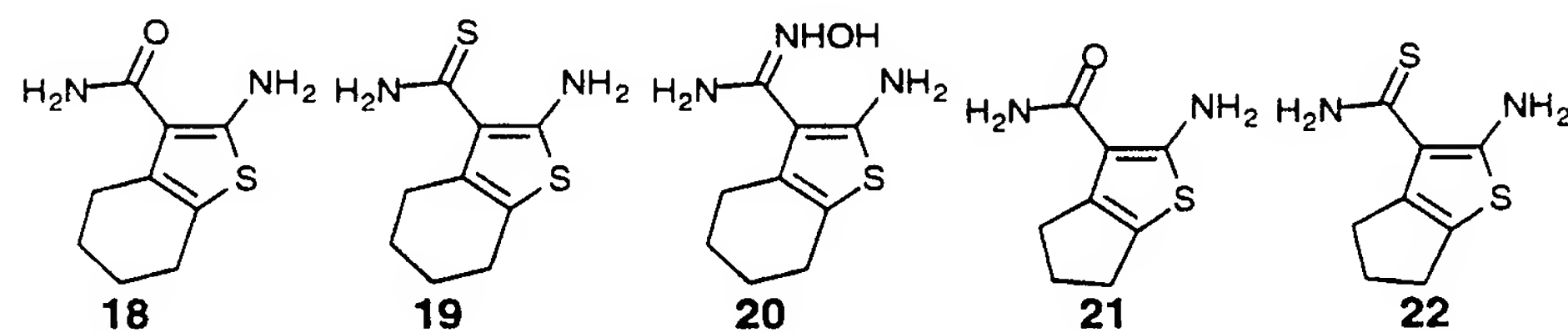


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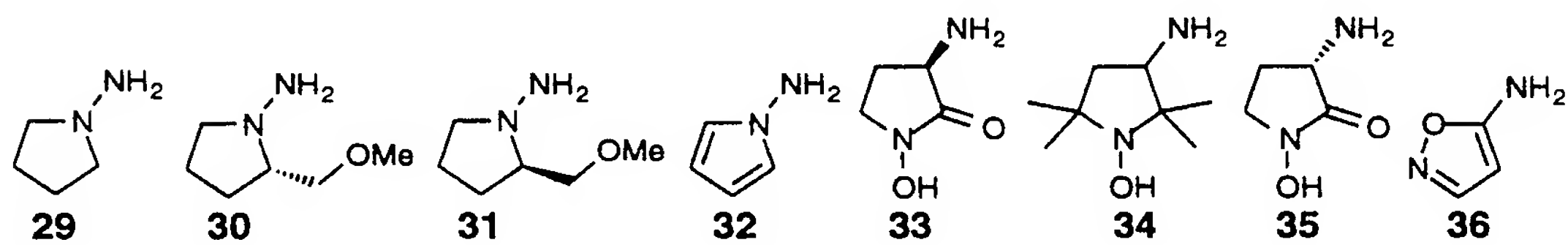


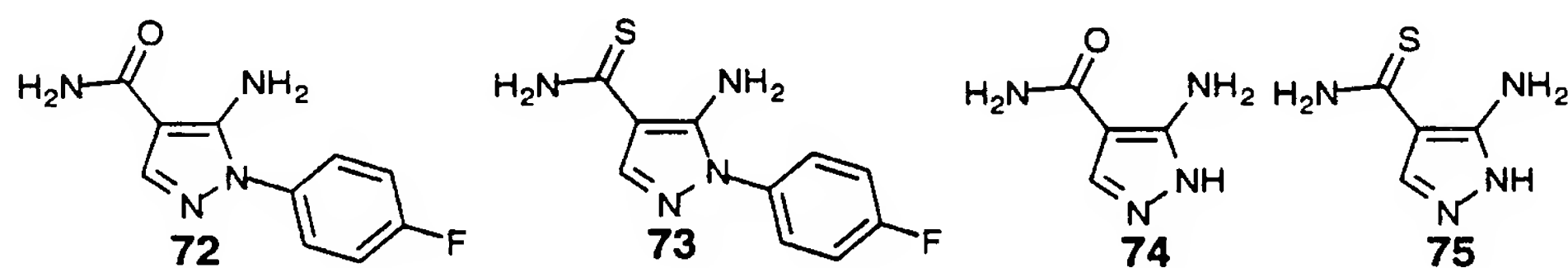
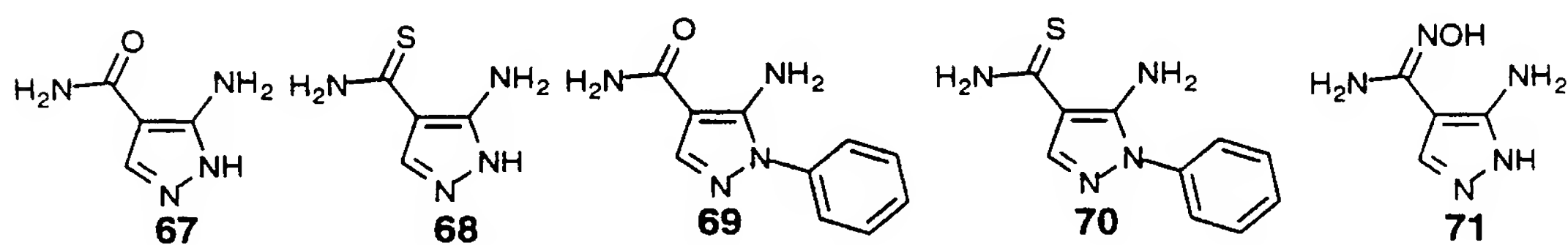
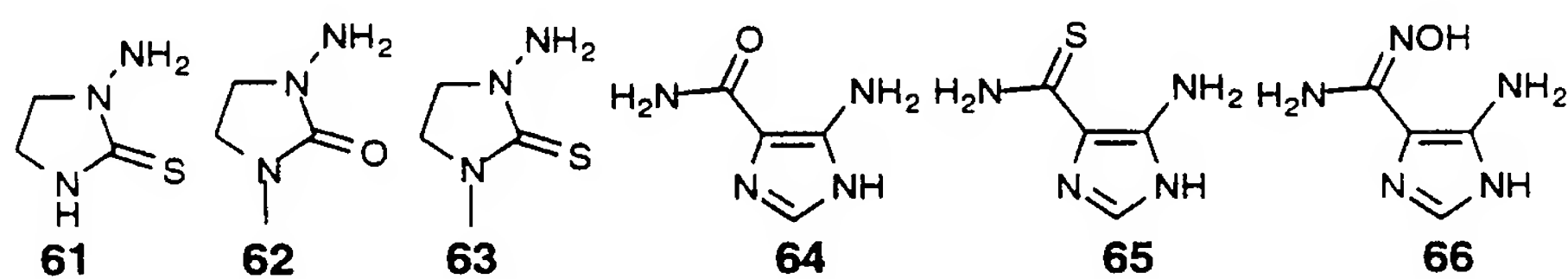
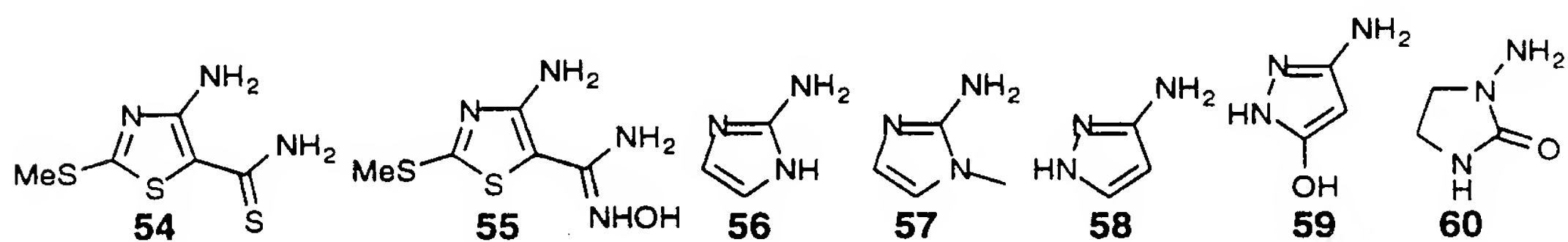
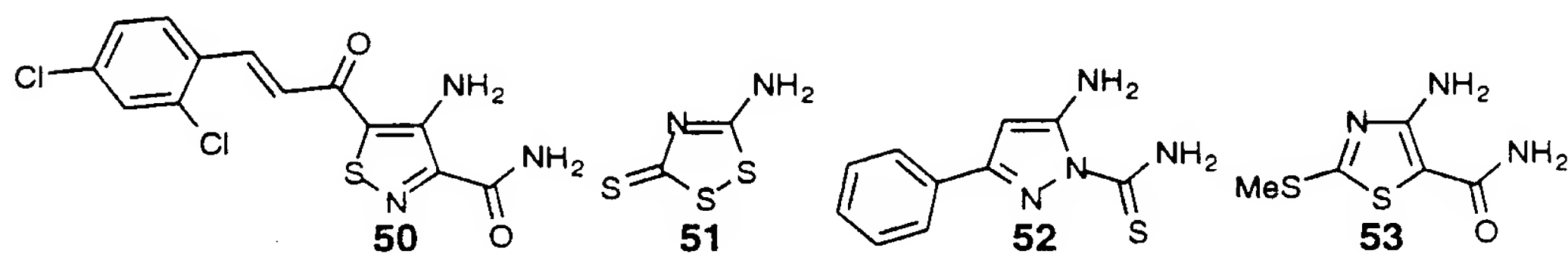
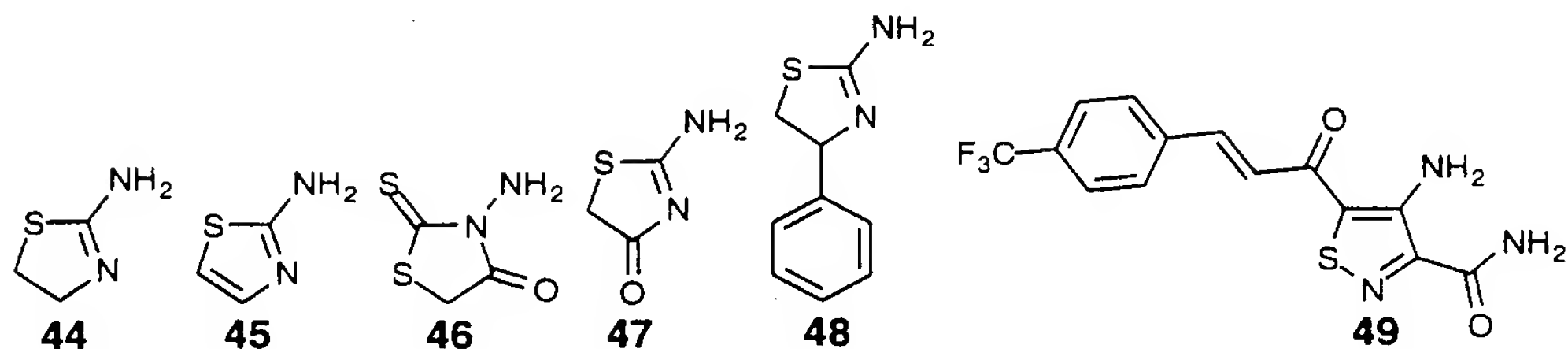
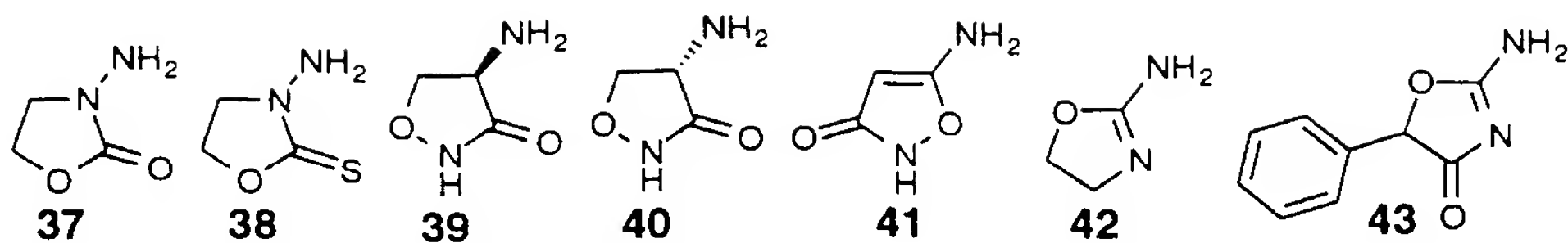
2610 Table 12. Amines of the type A-NH<sub>2</sub>

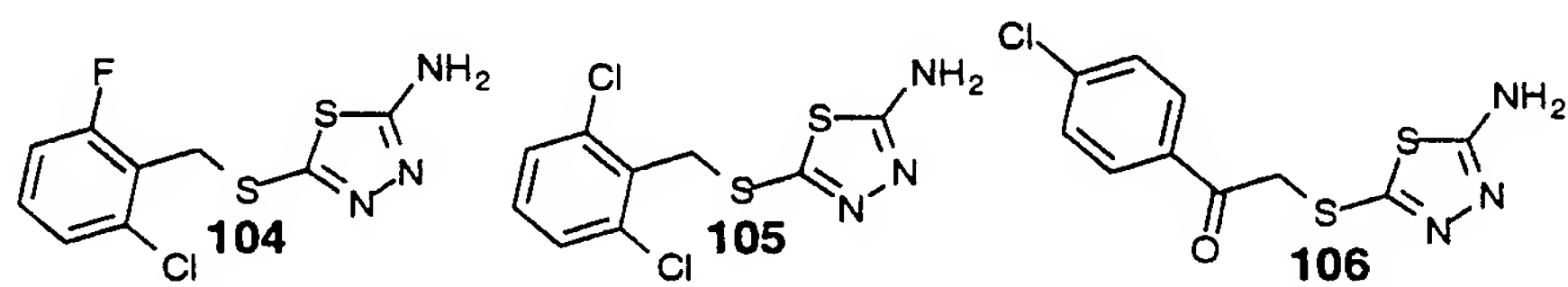
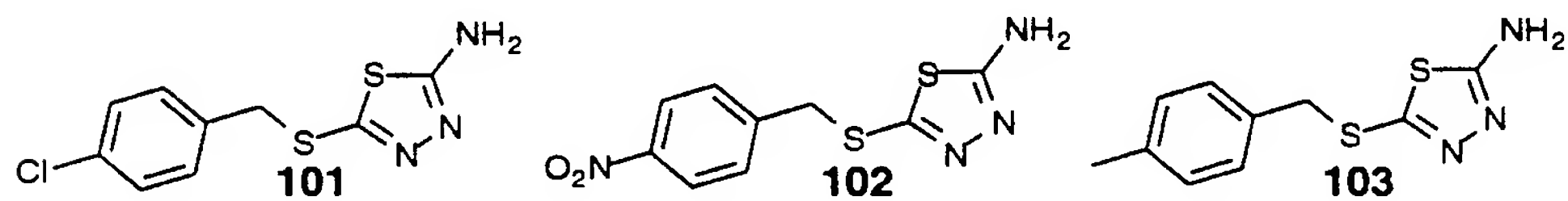
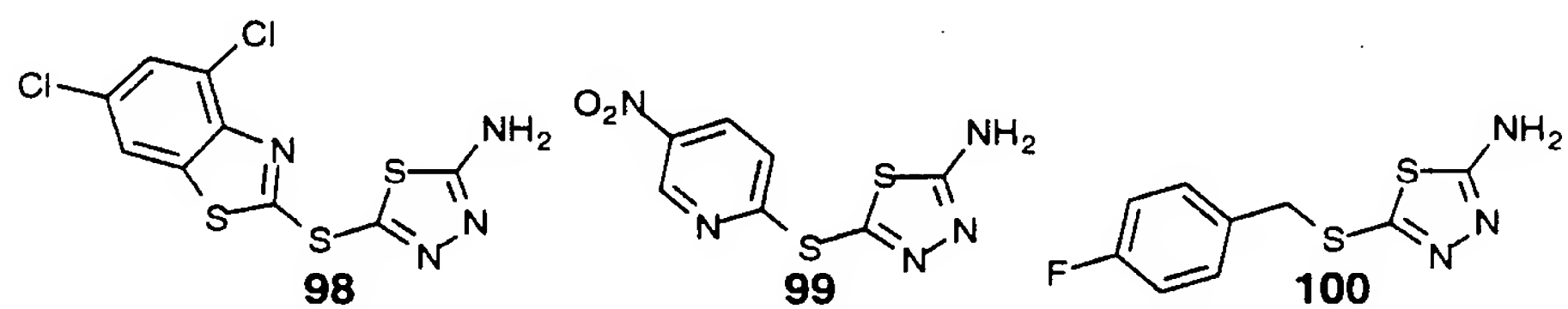
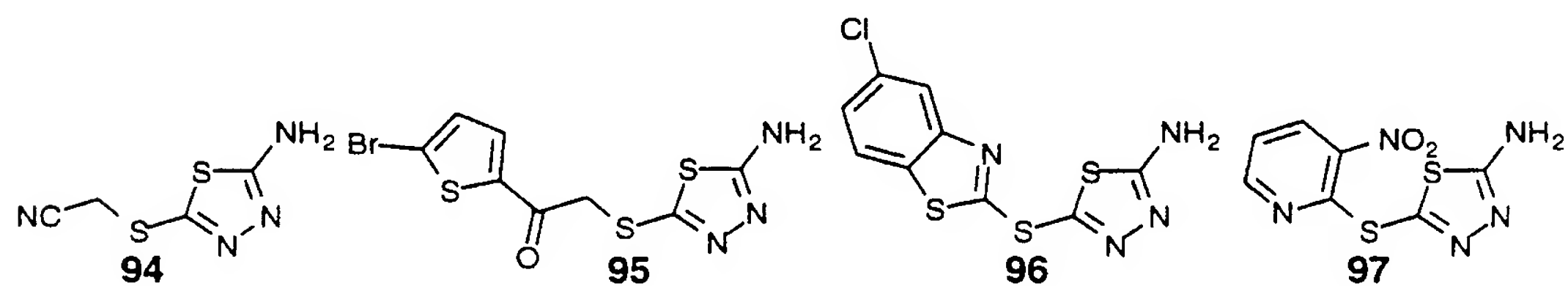
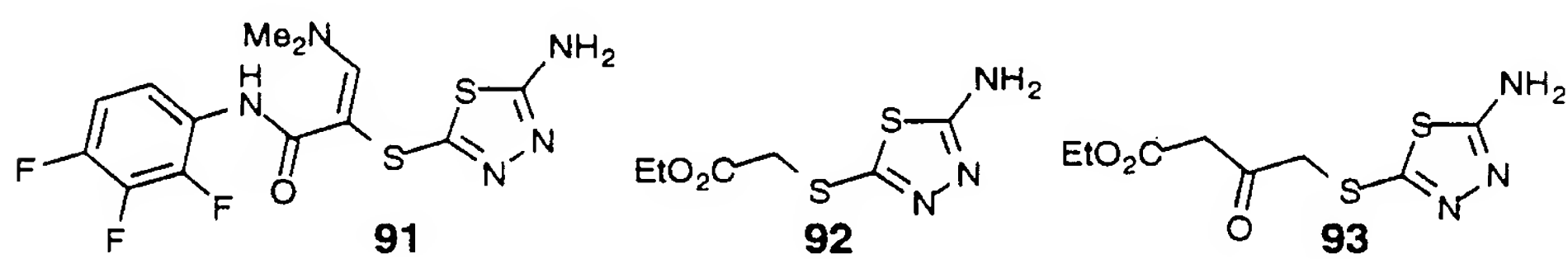
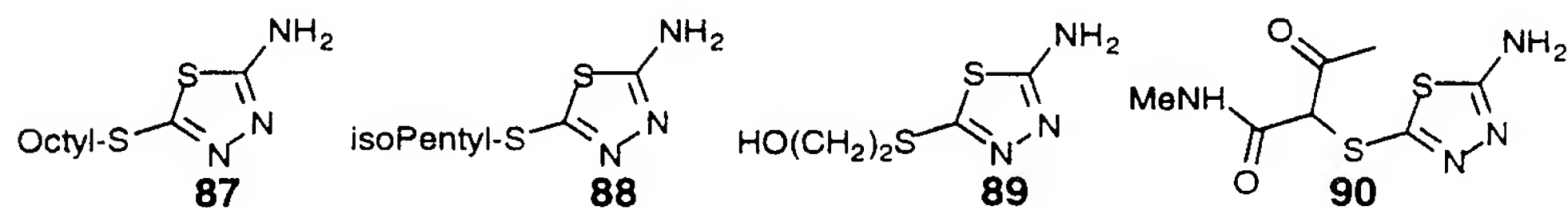
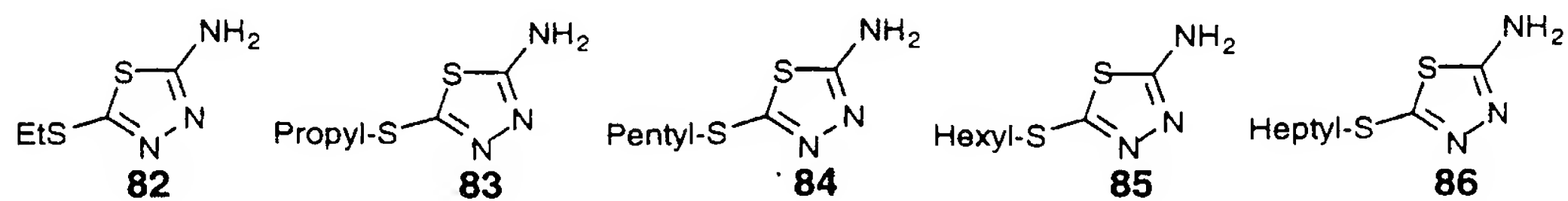
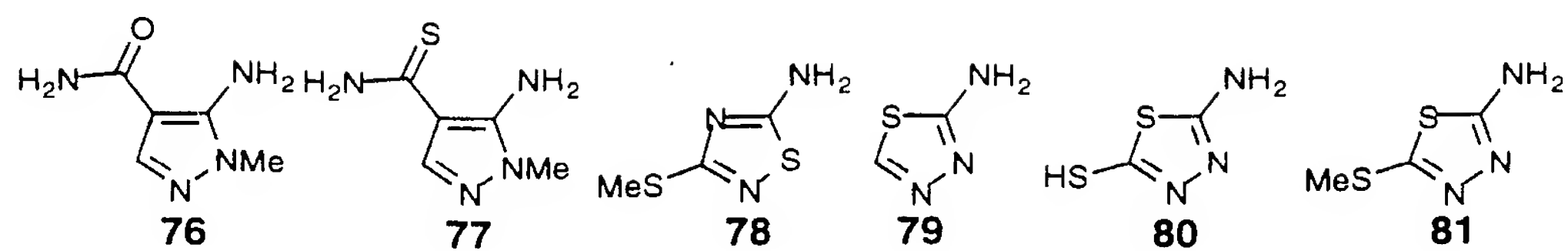
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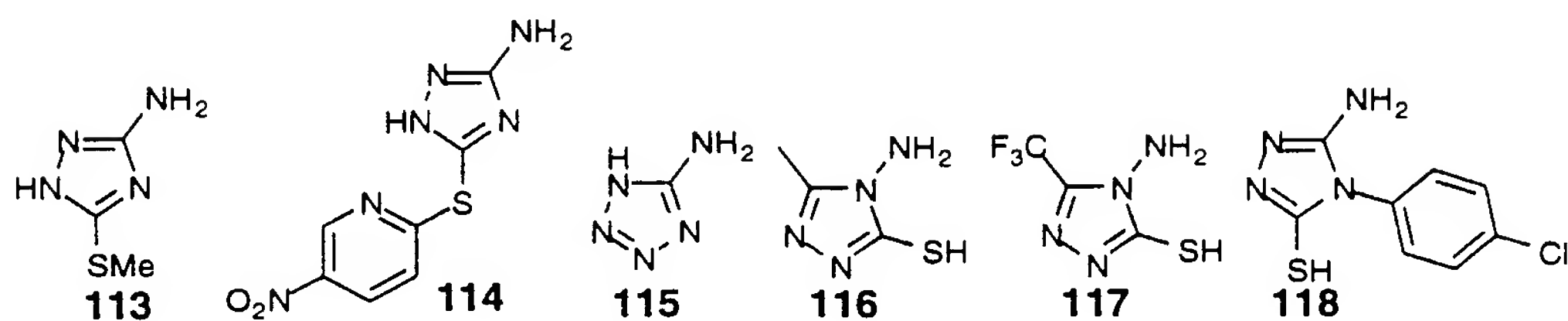
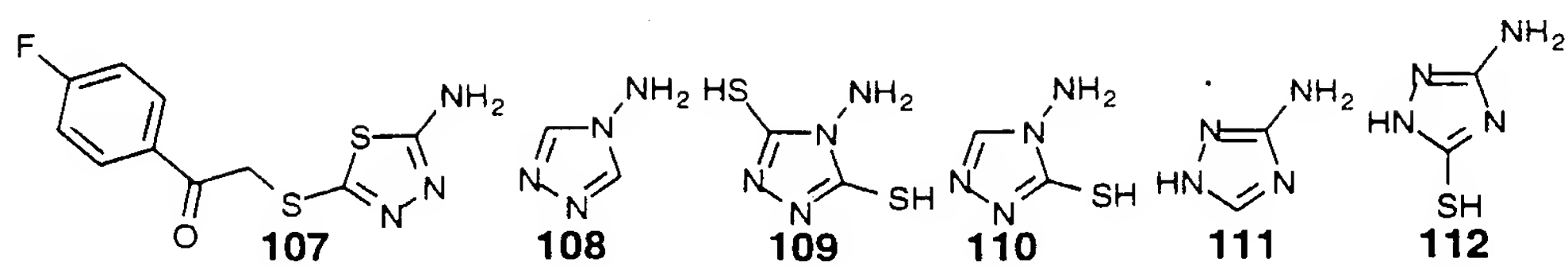


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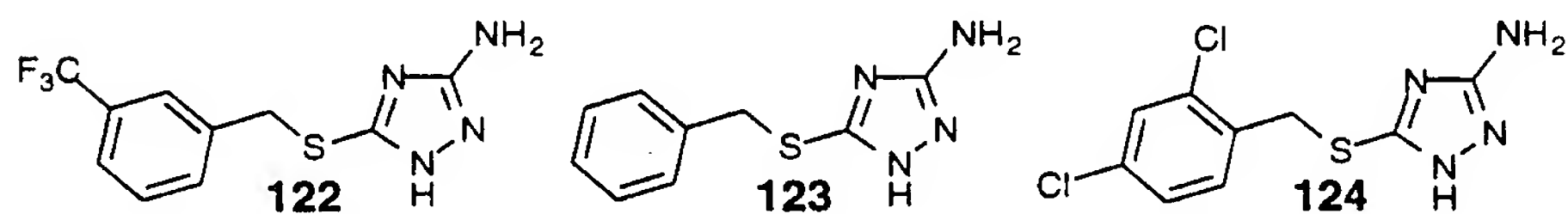
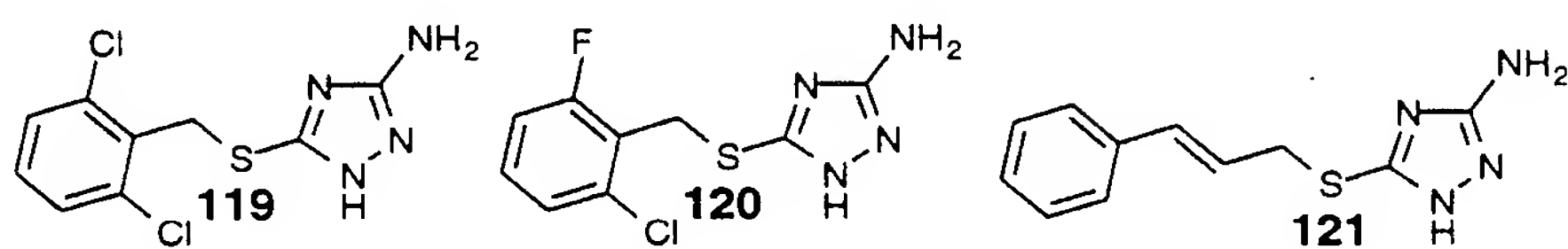




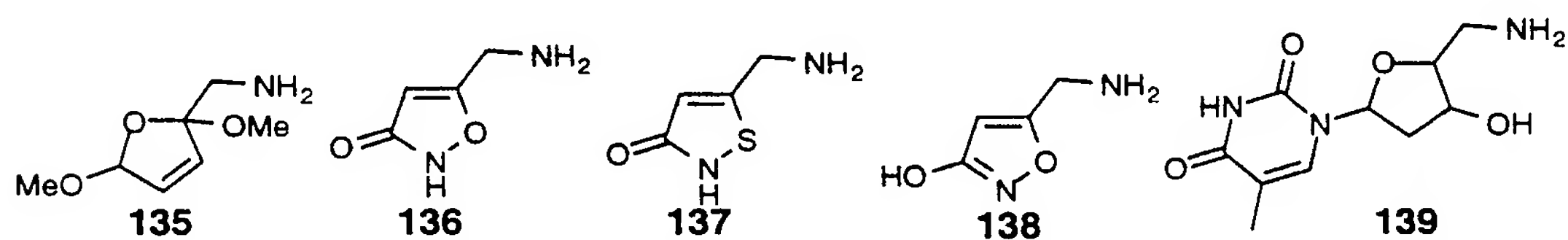
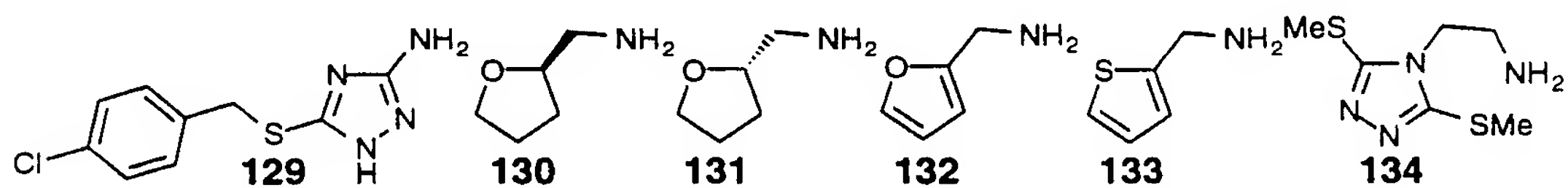
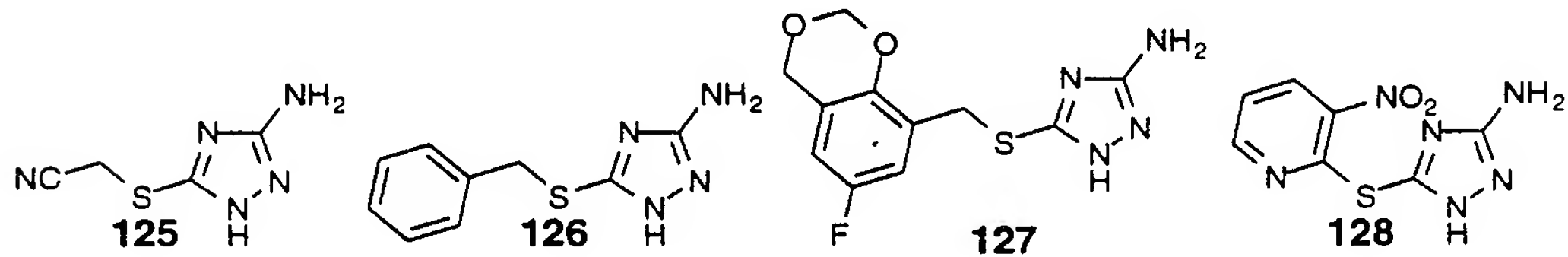




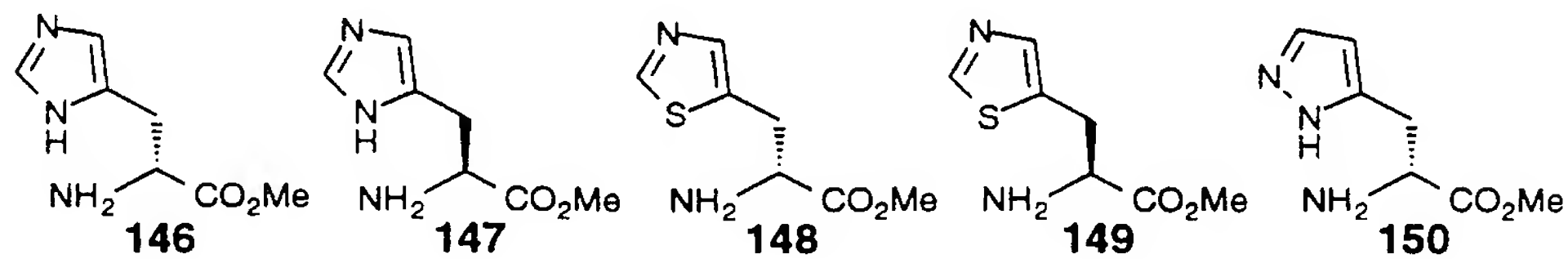
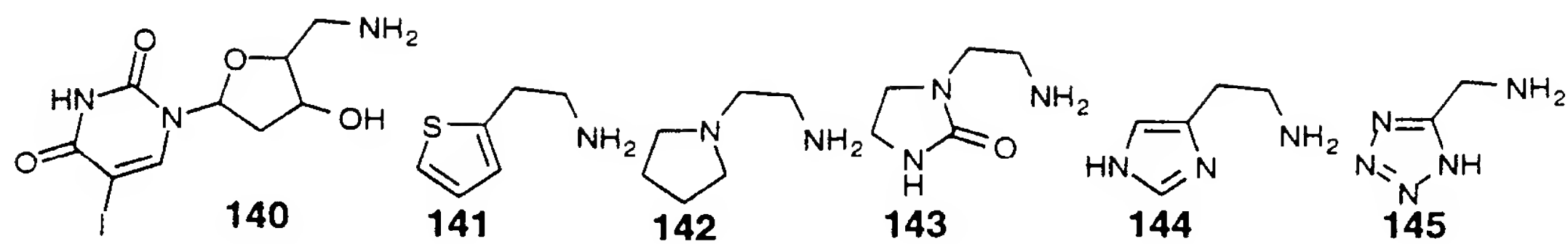
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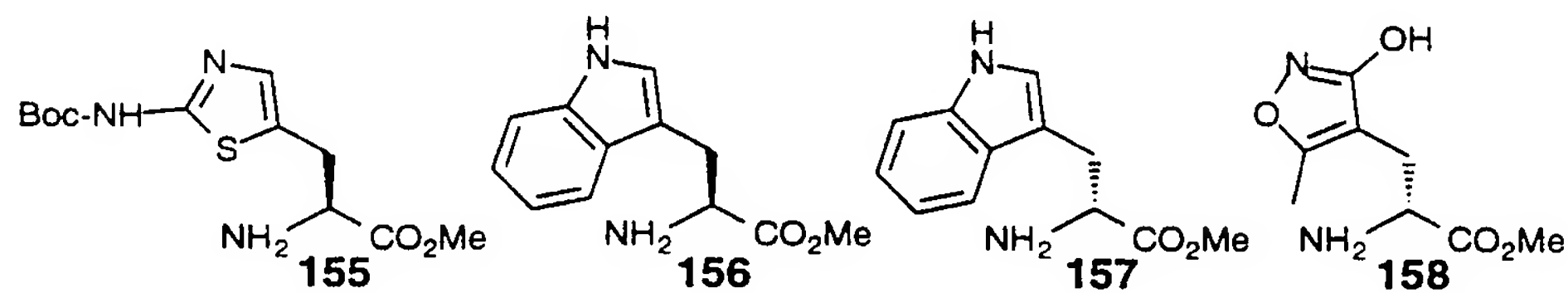
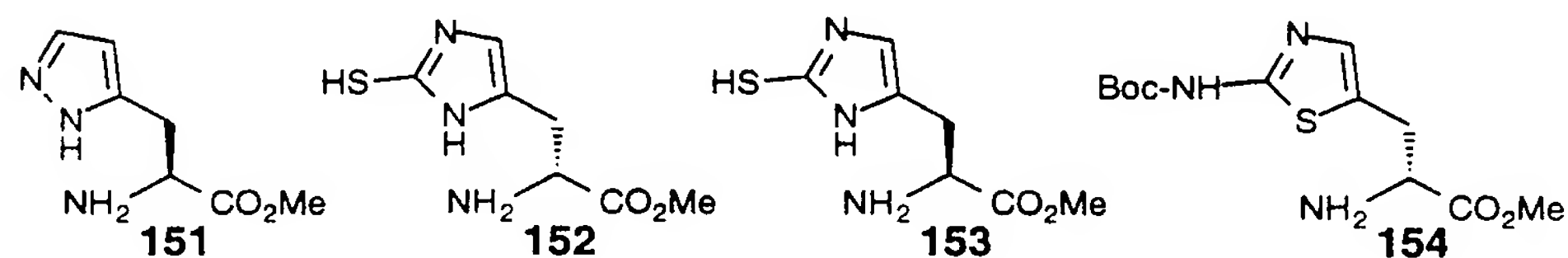
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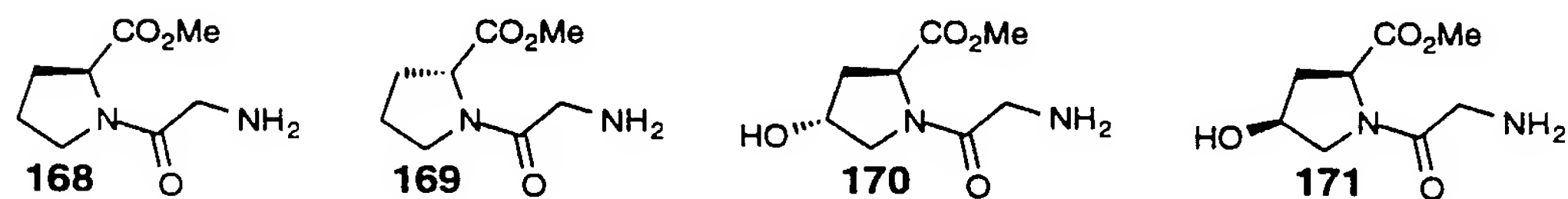
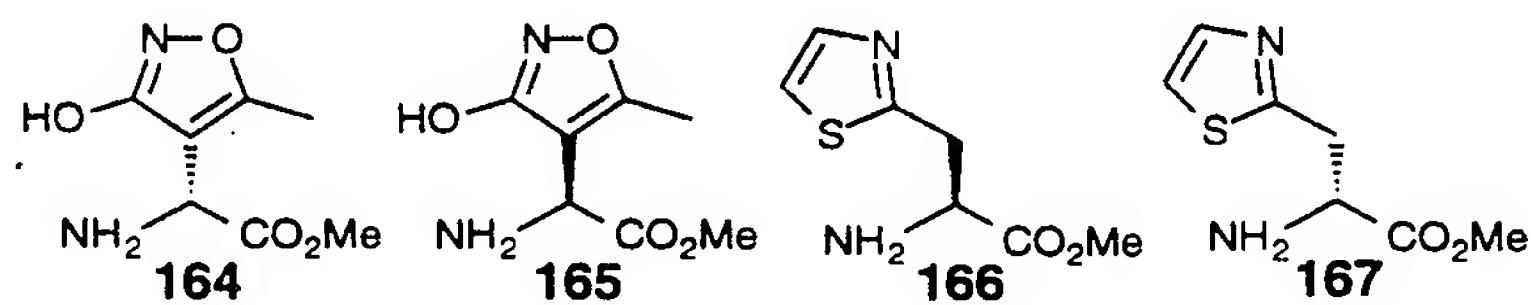
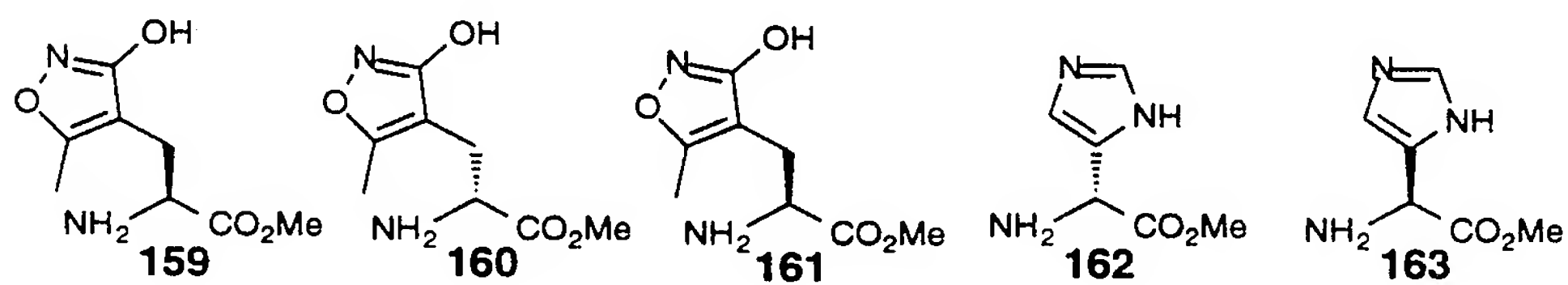
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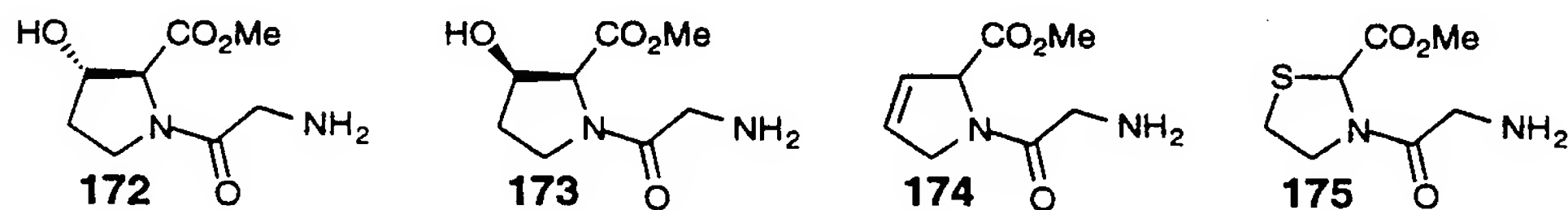
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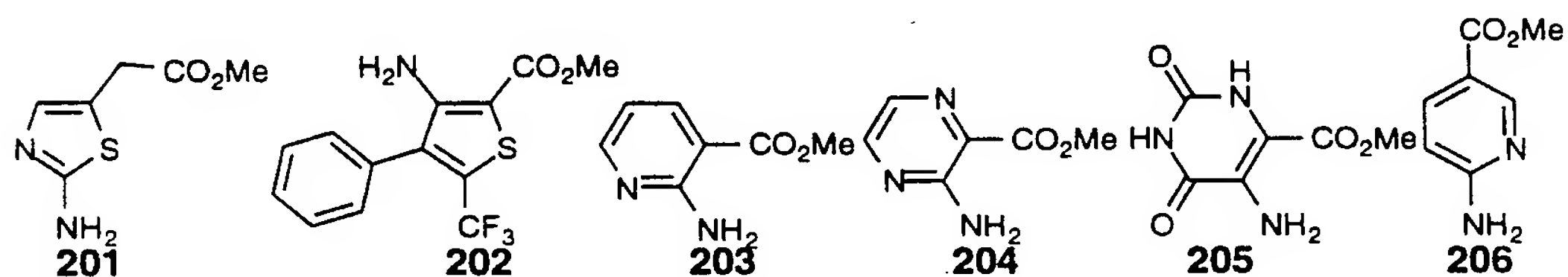
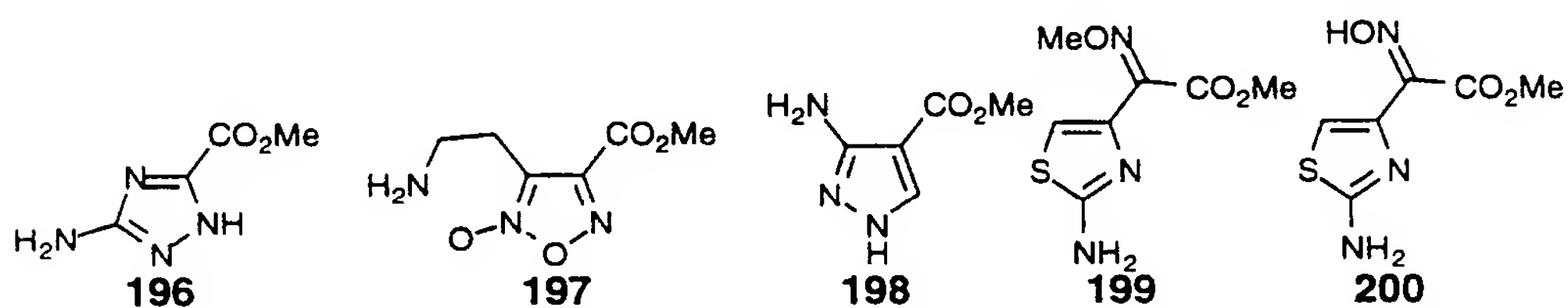
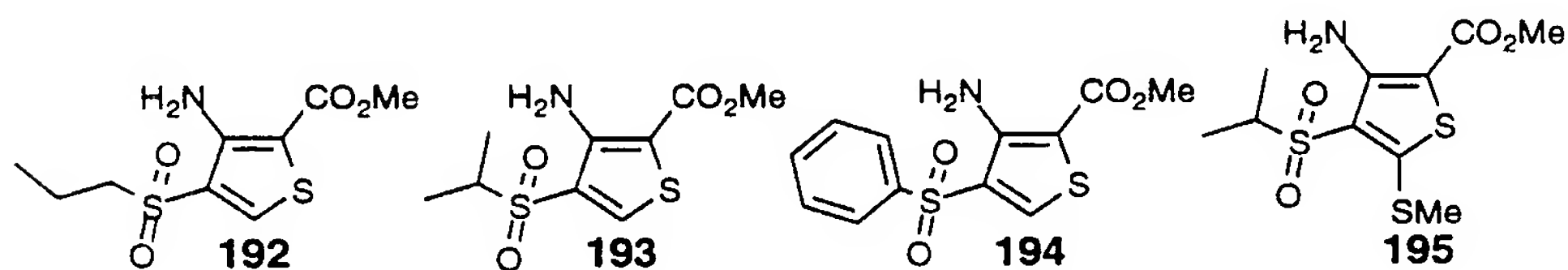
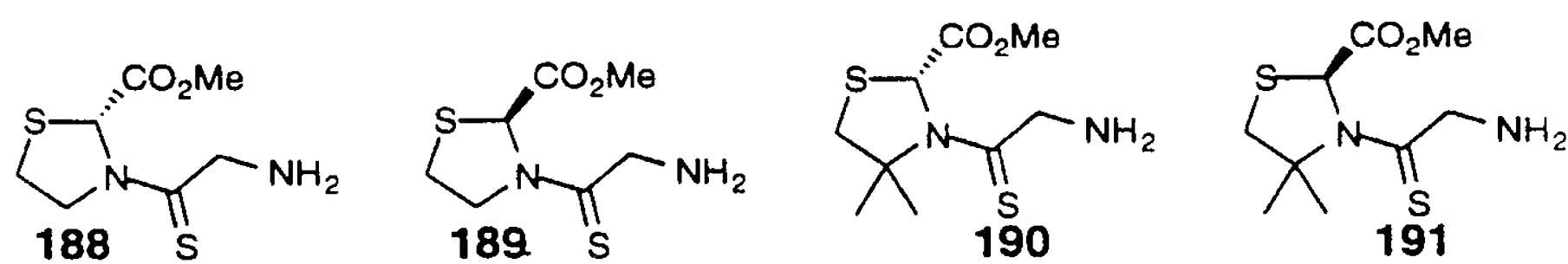
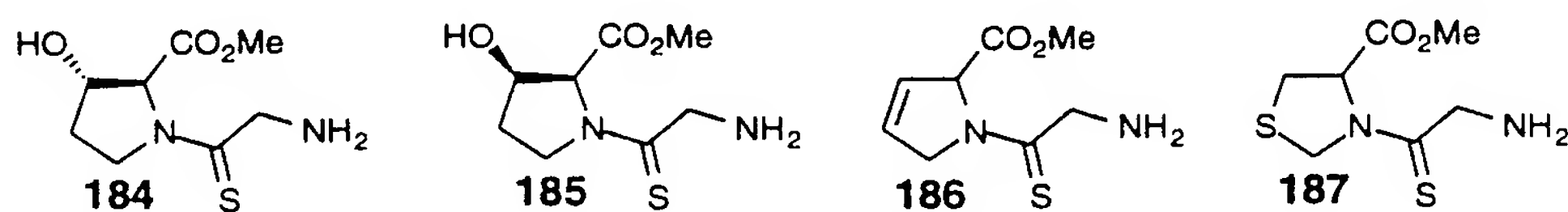
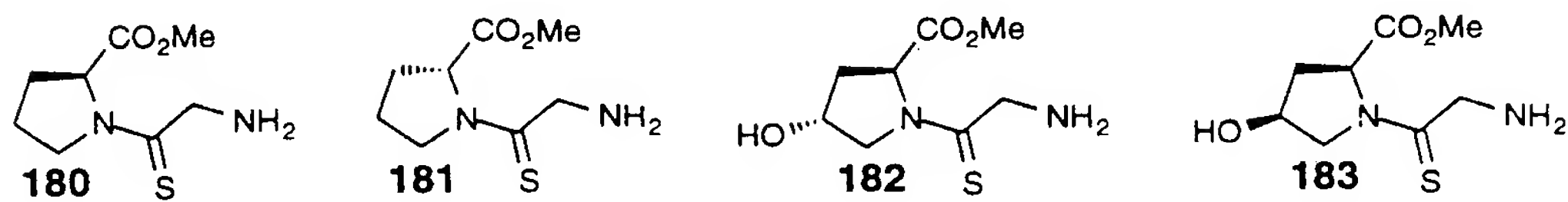
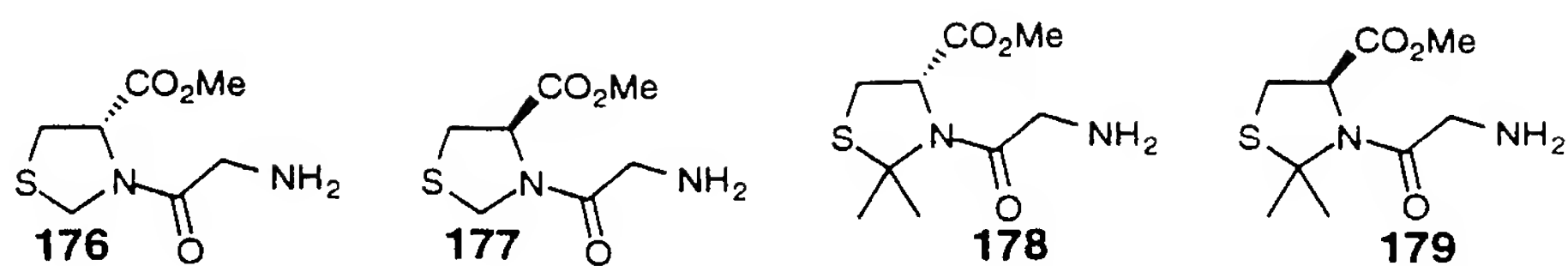
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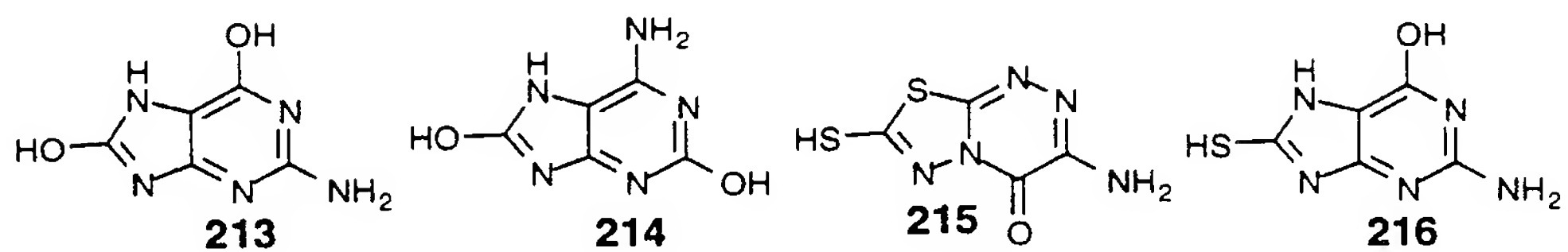
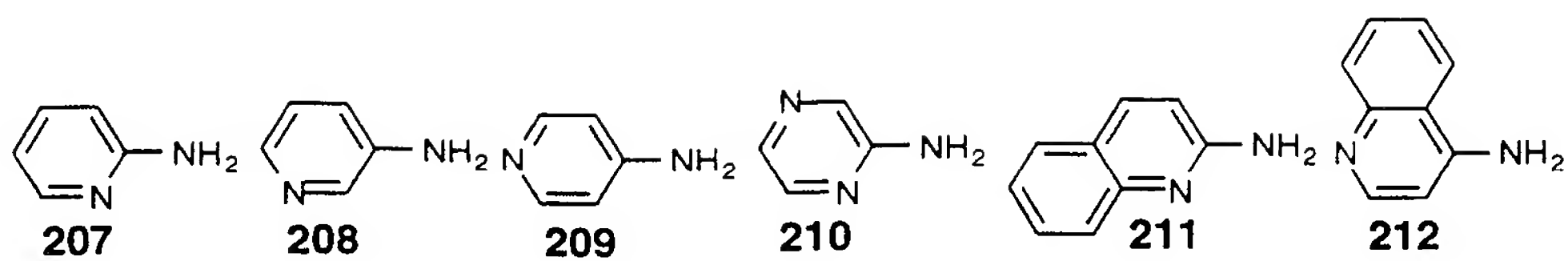


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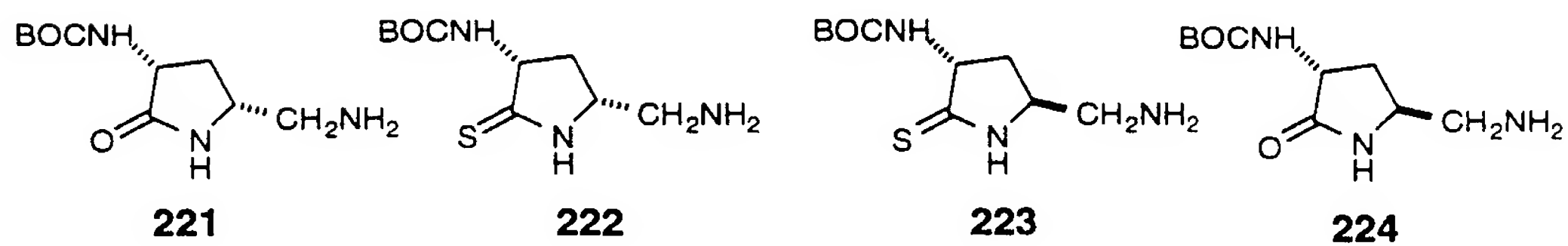
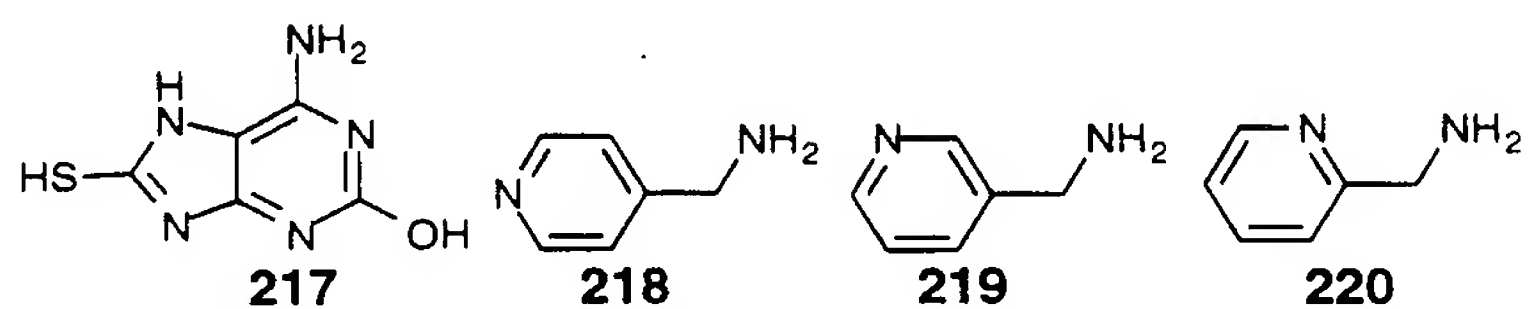




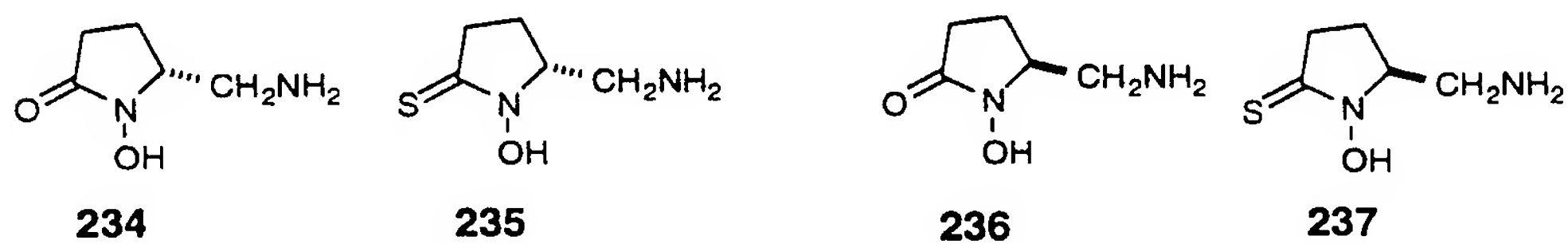
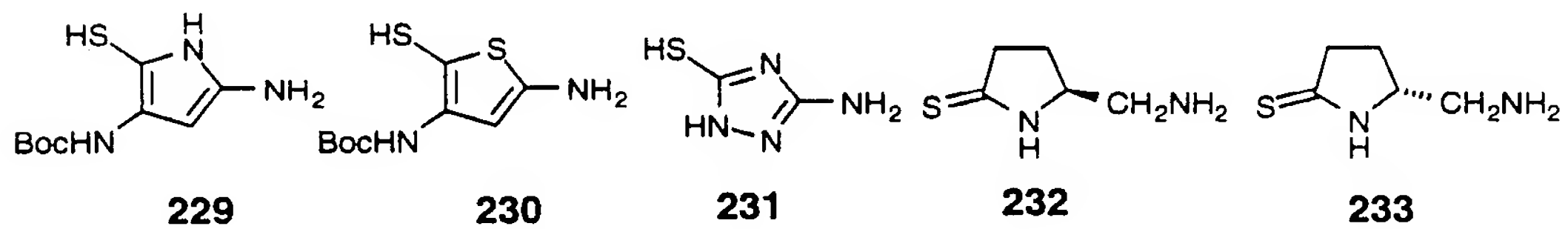
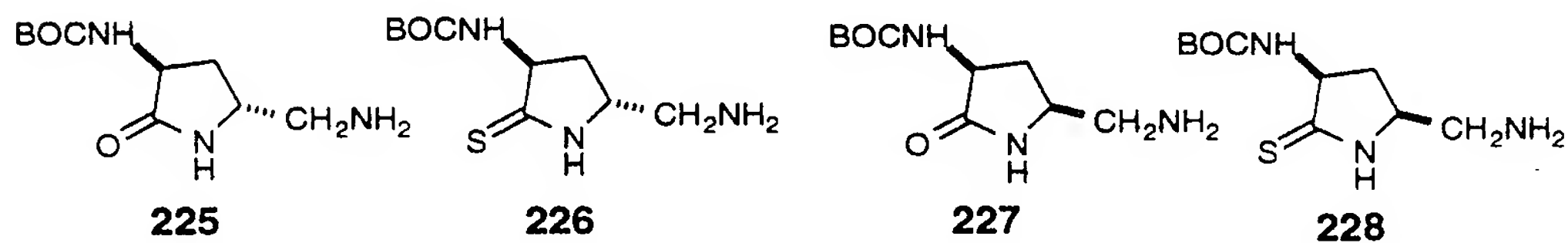




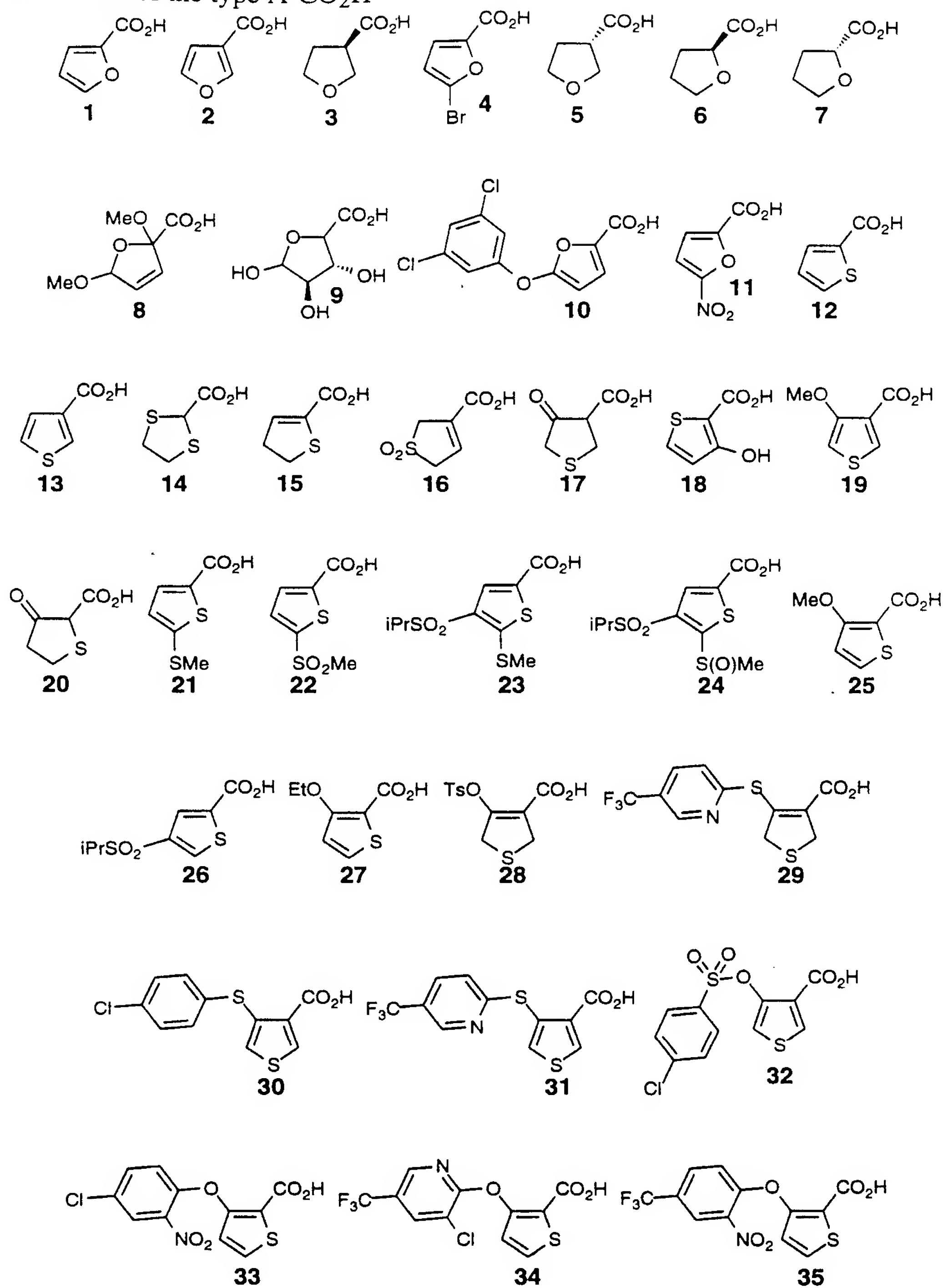
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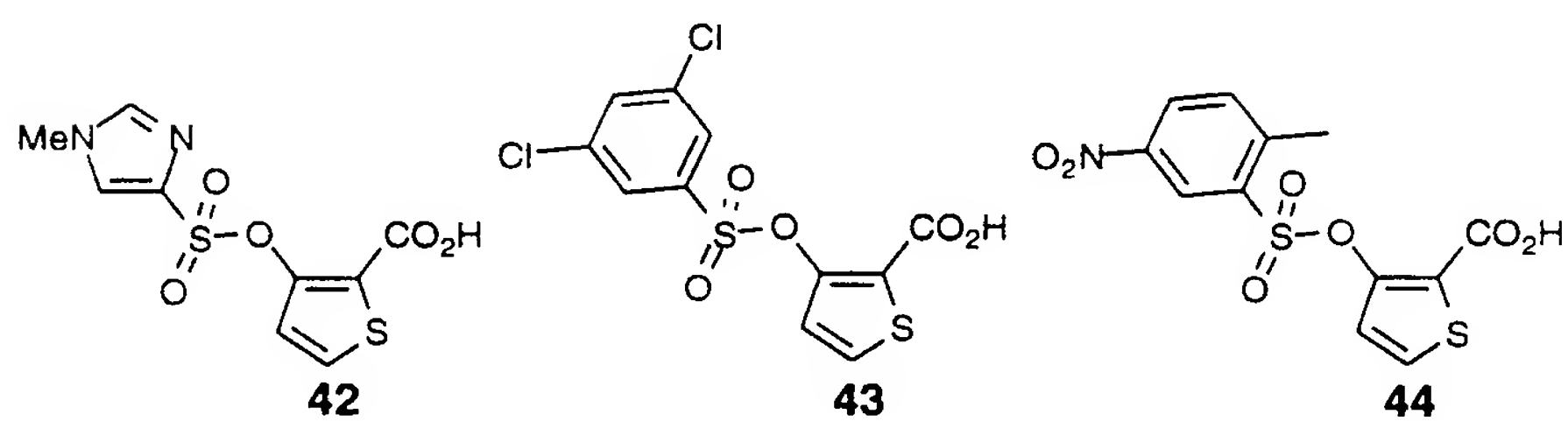
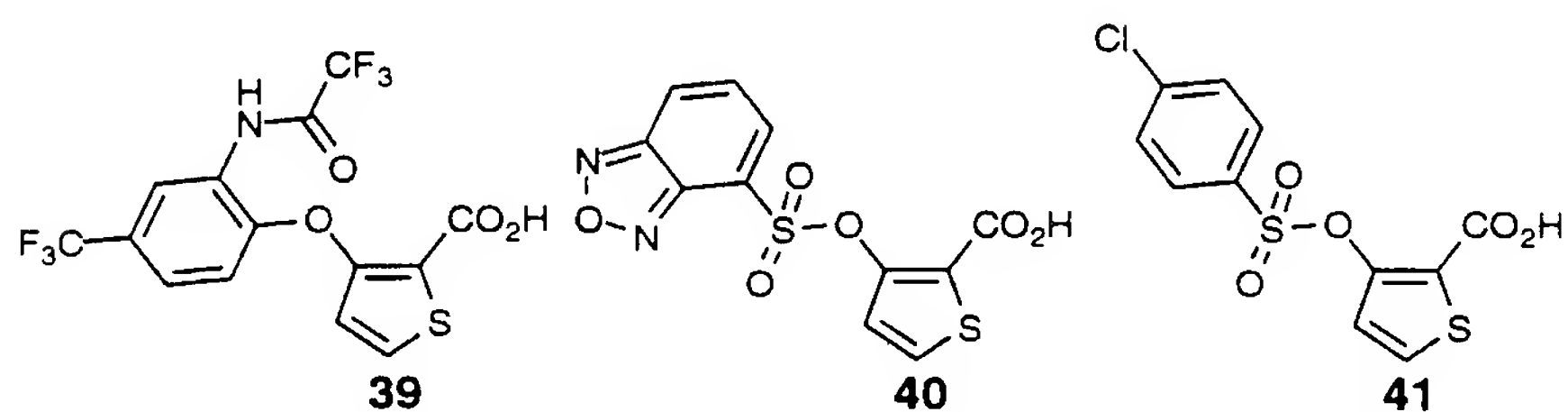
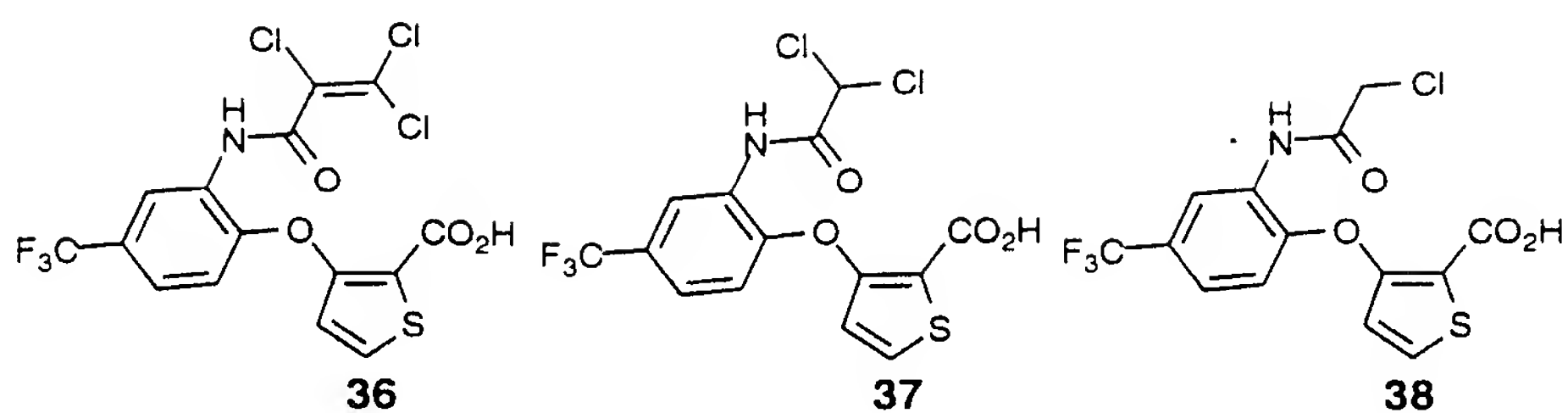


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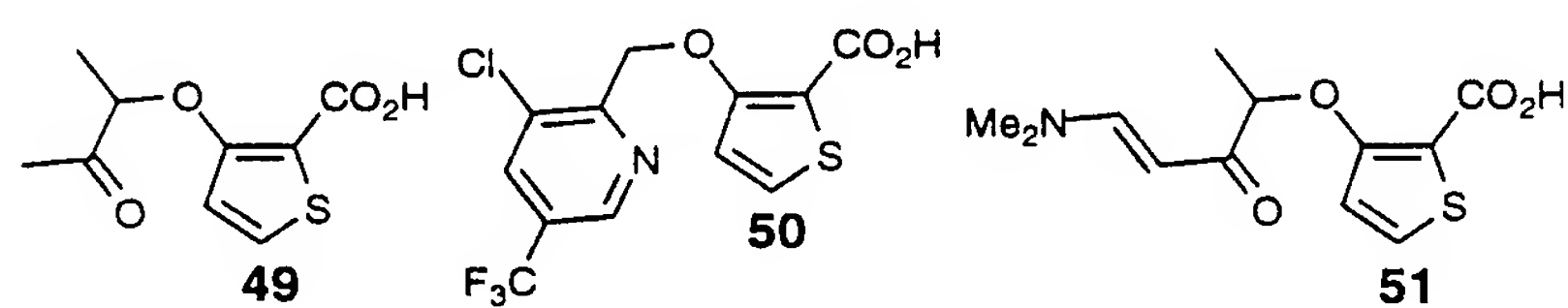
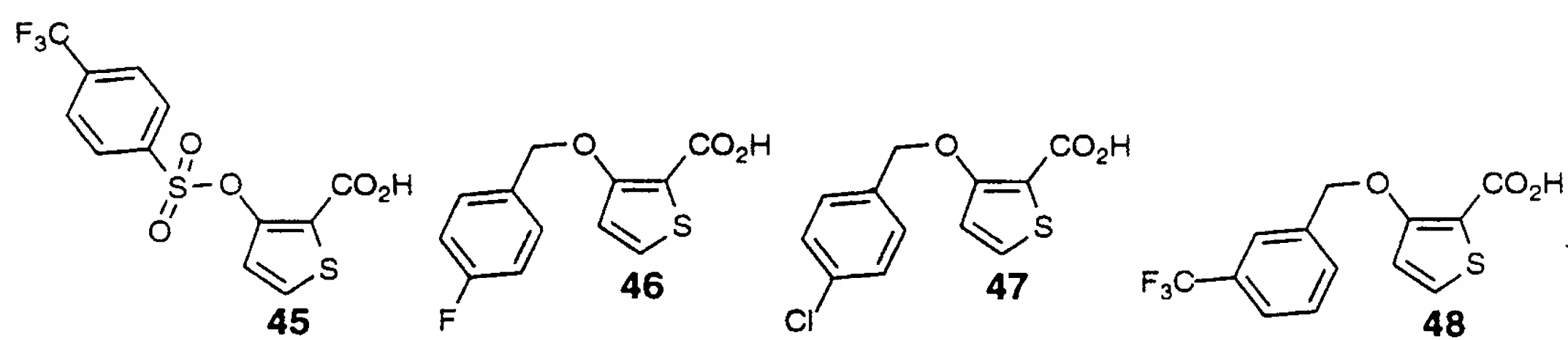


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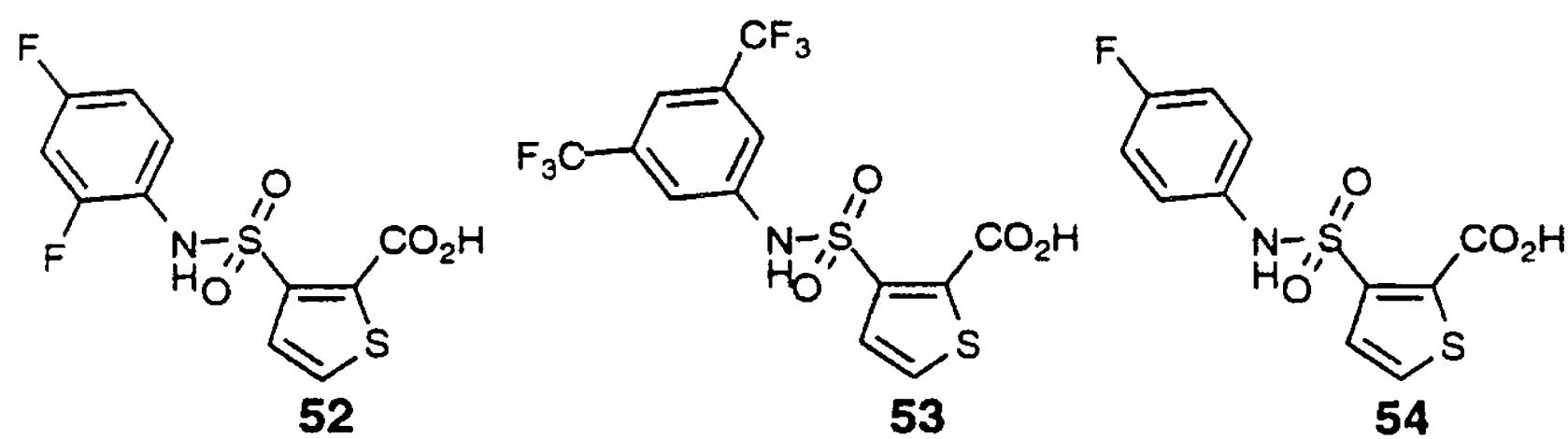
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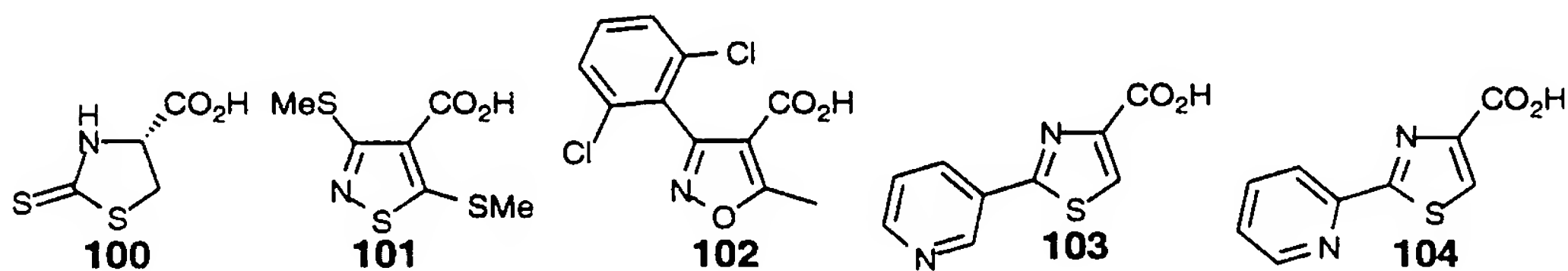
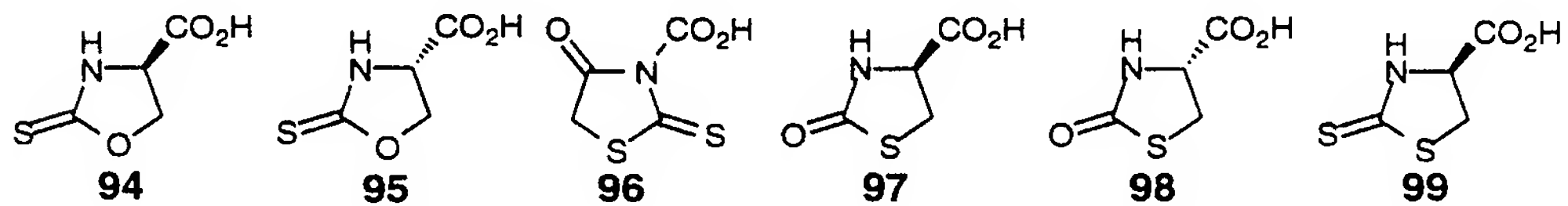
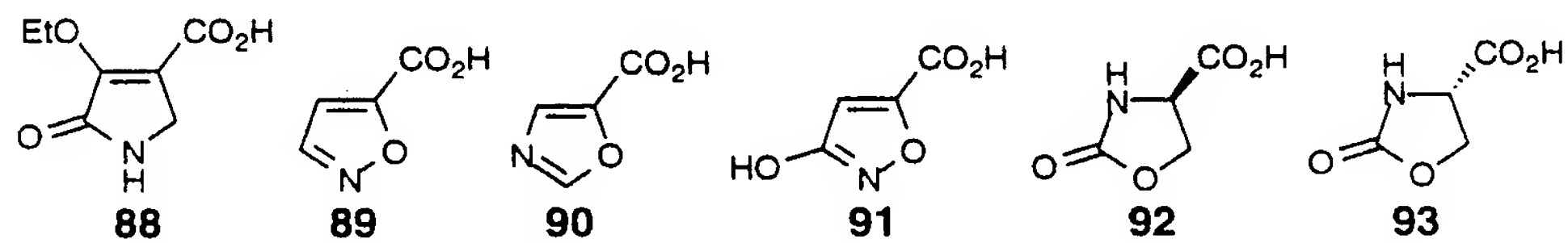
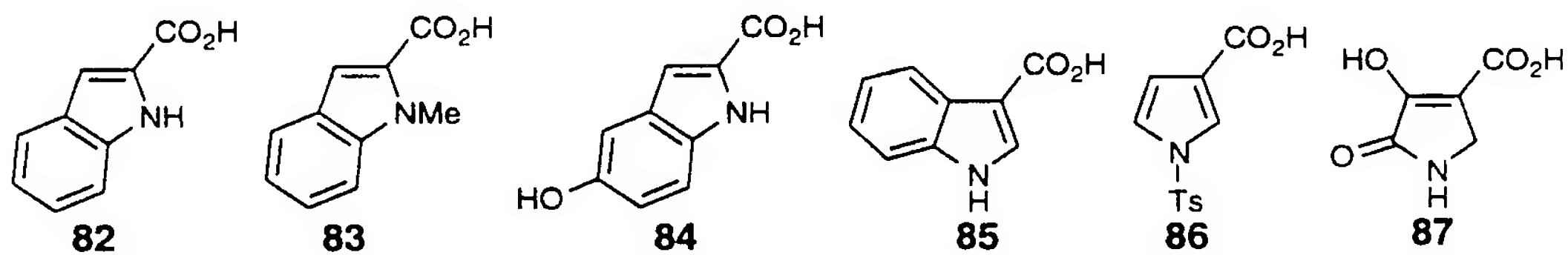
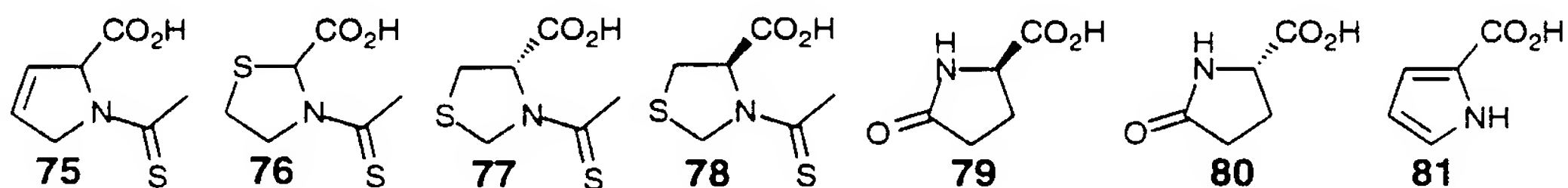
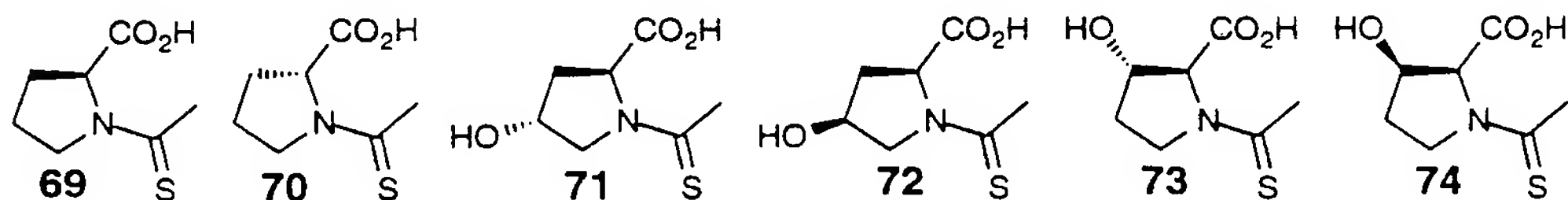
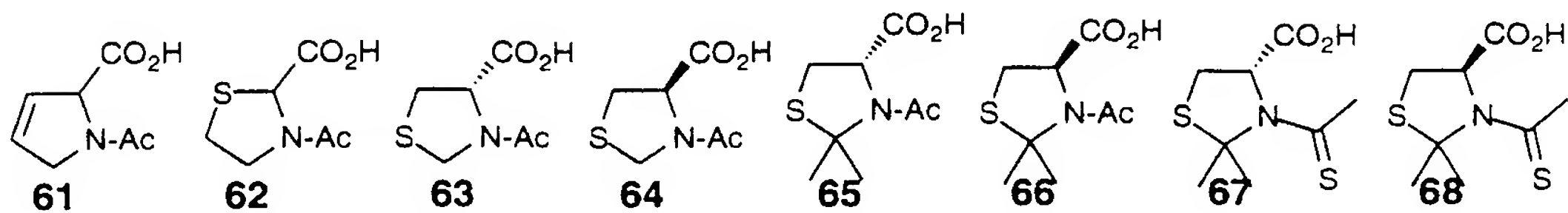
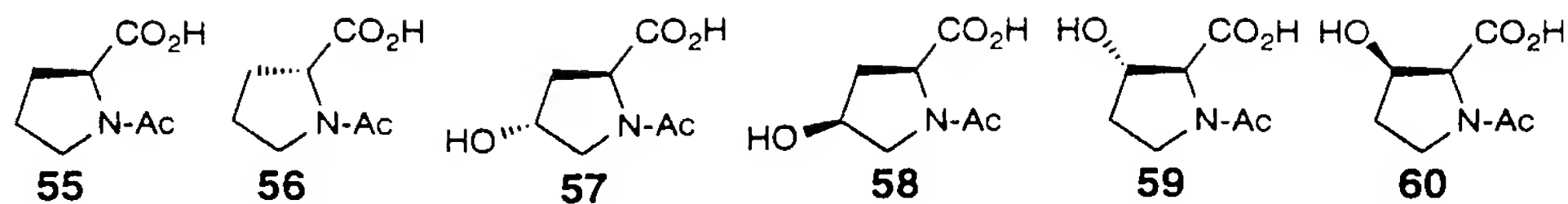


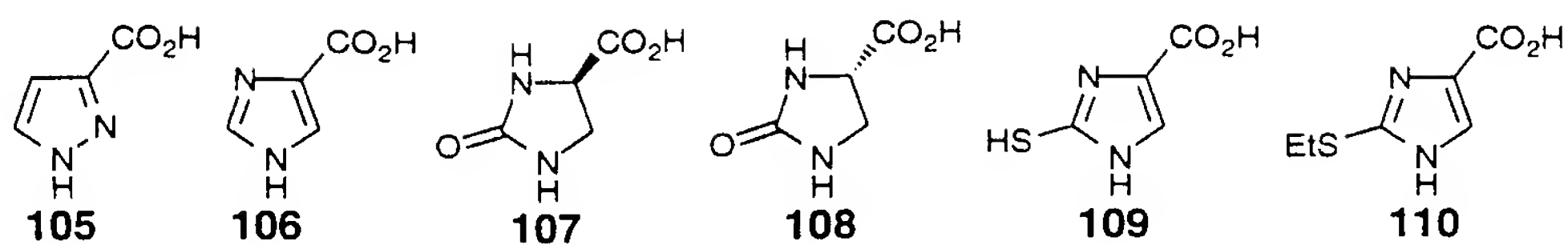
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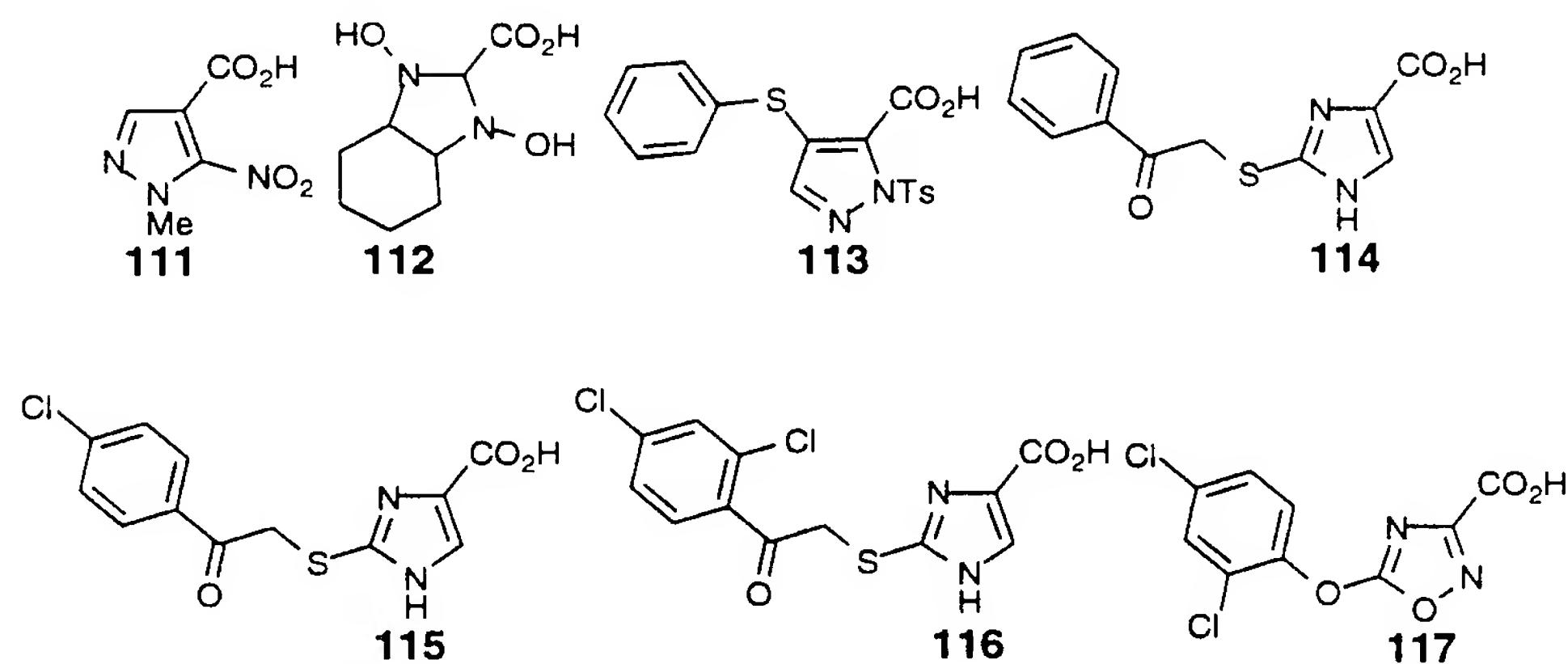
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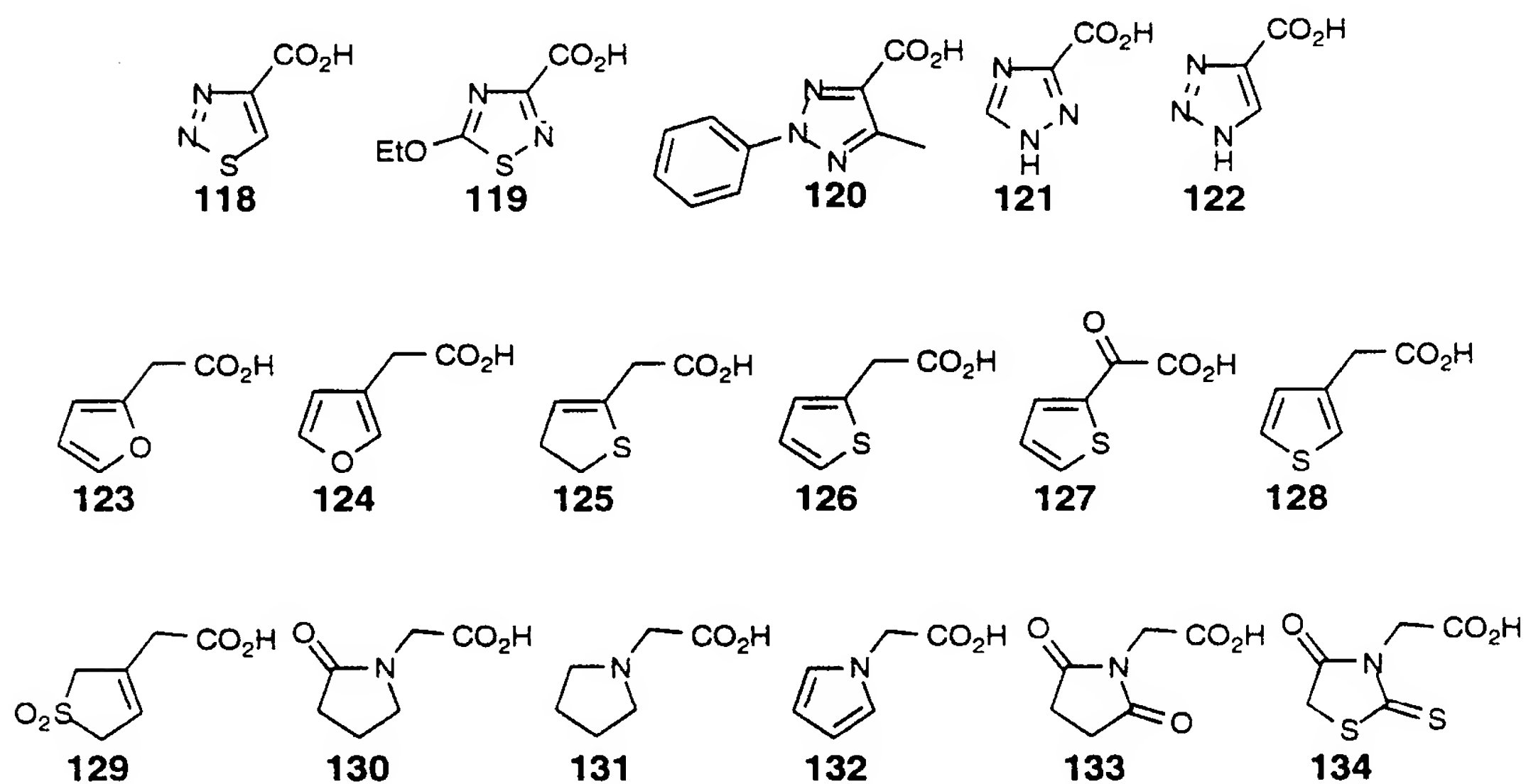




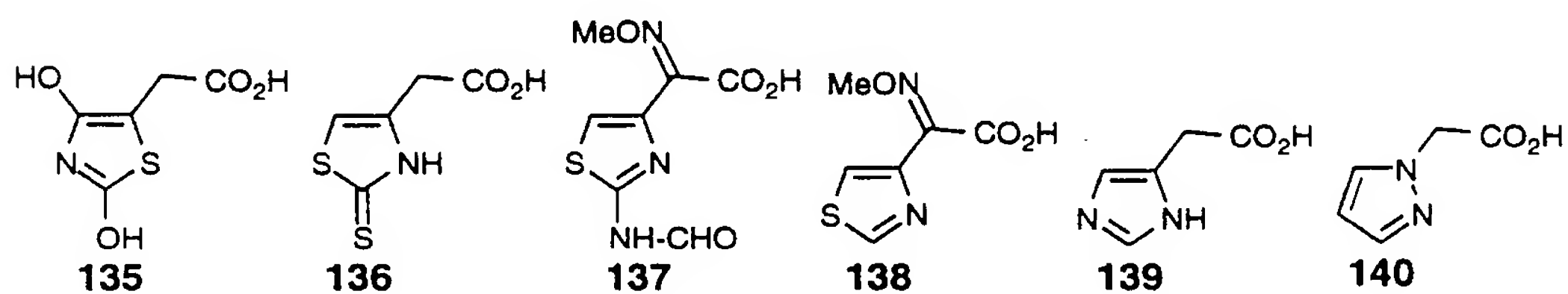
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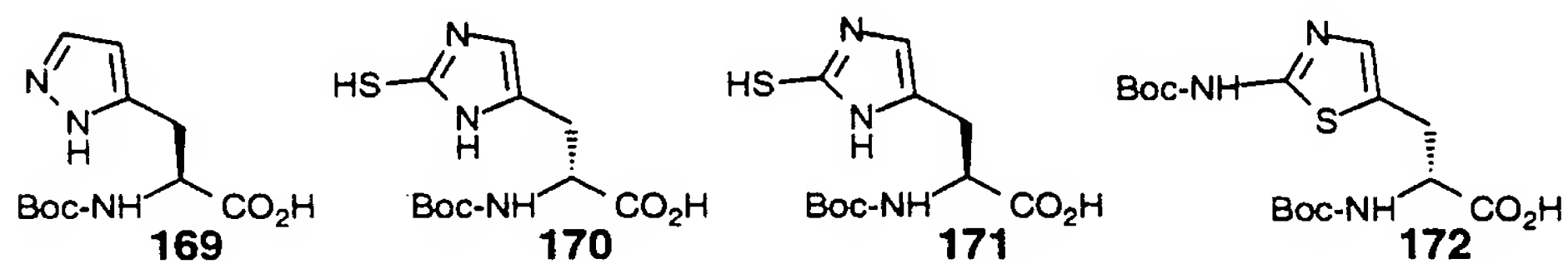
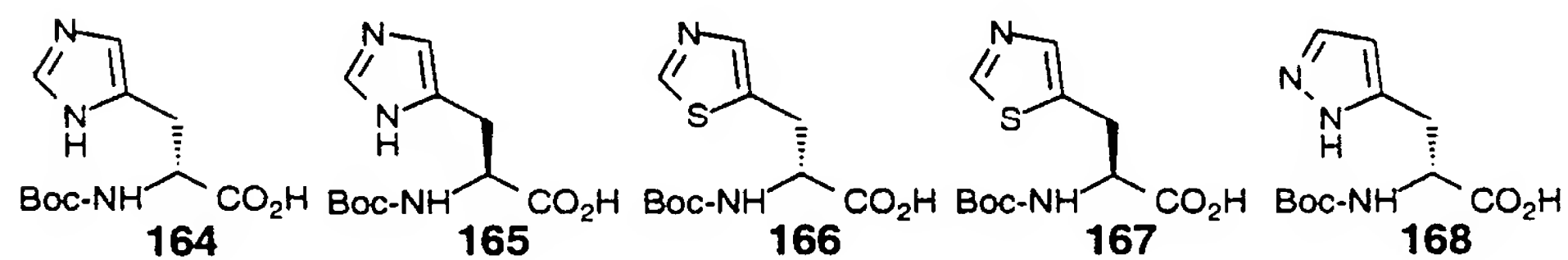
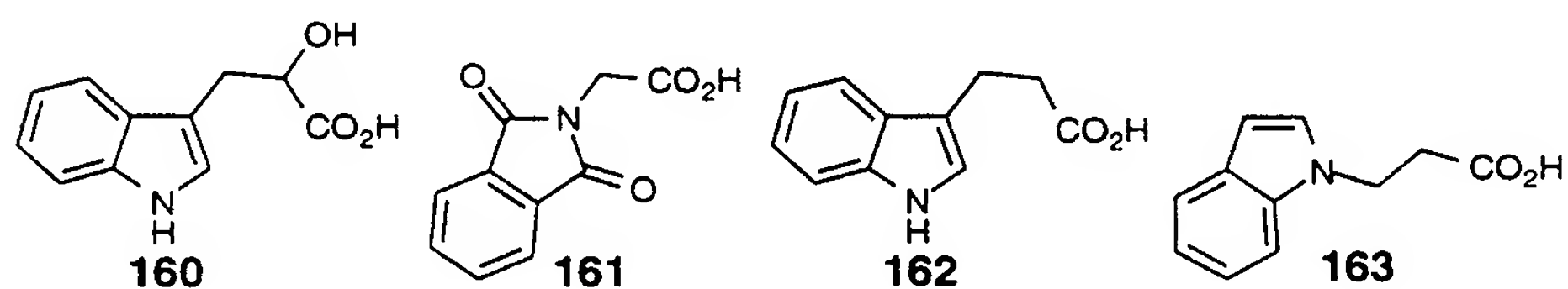
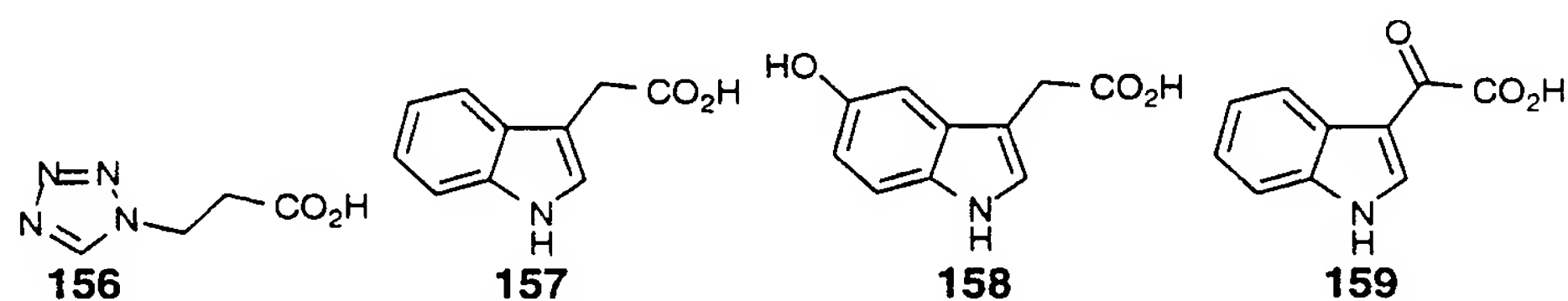
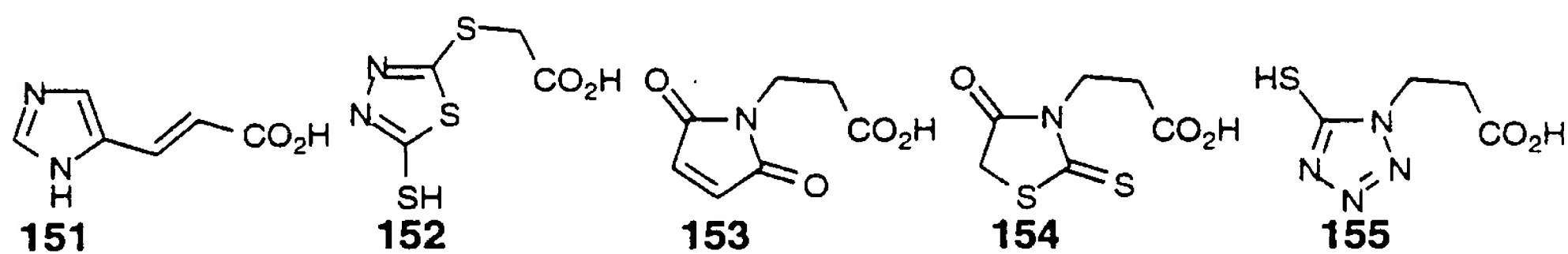
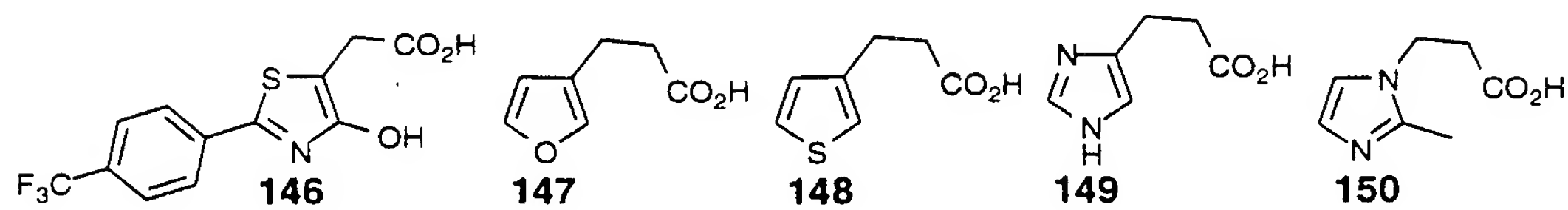
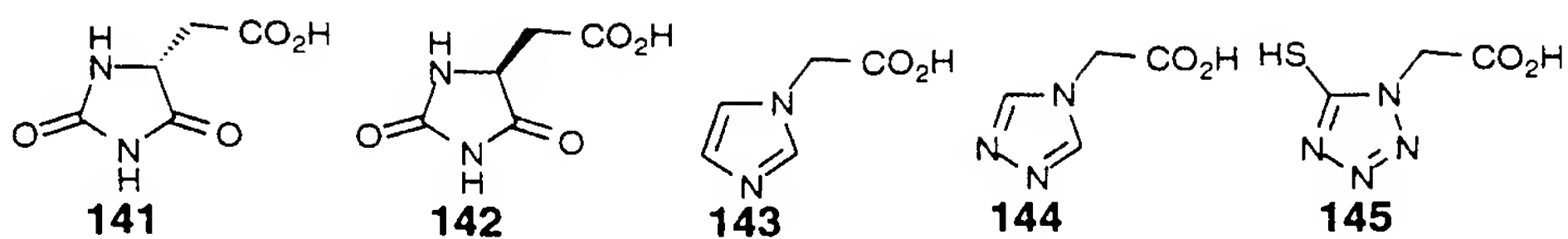


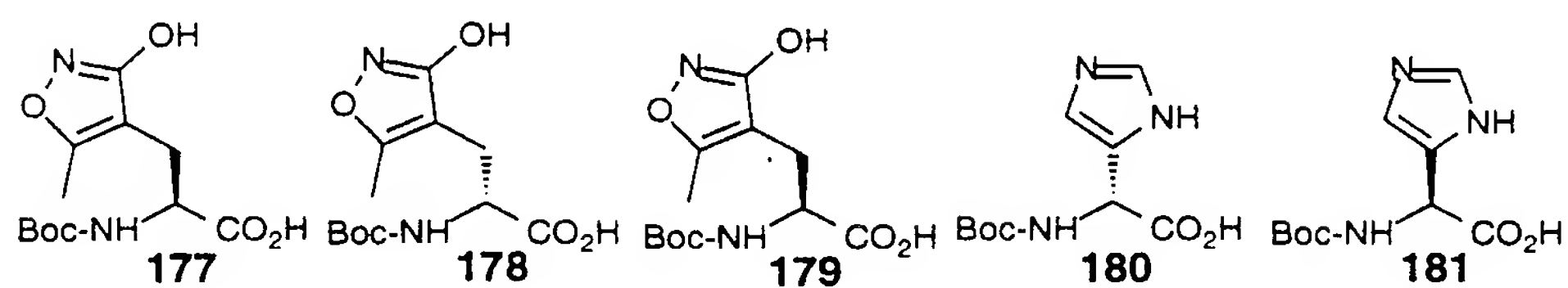
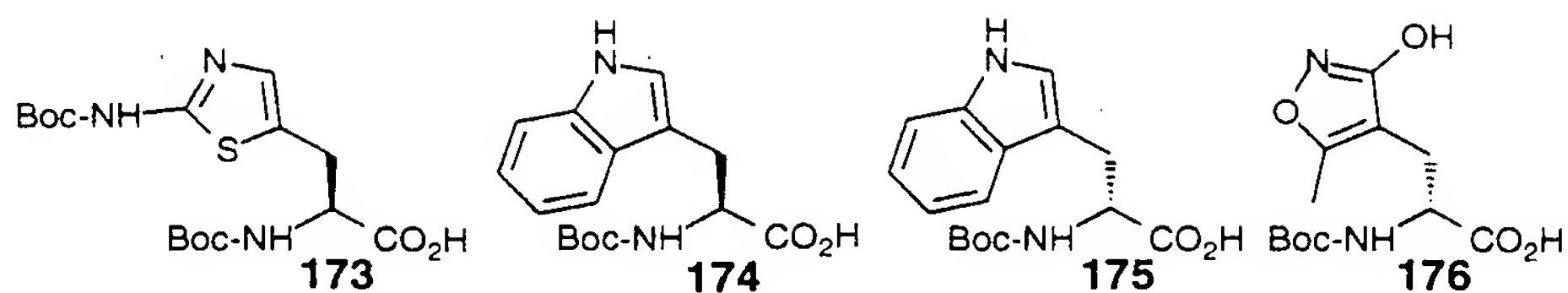
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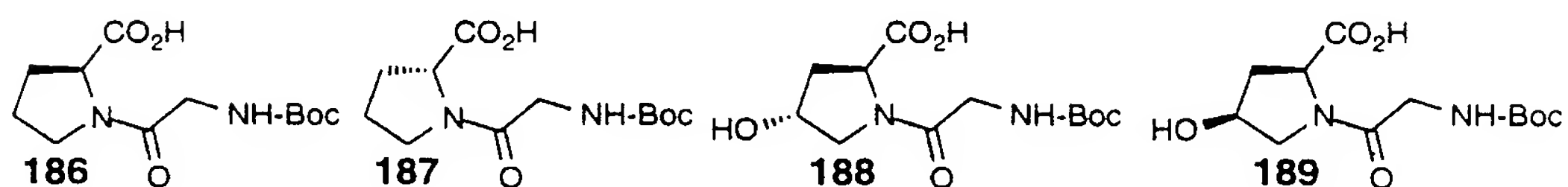
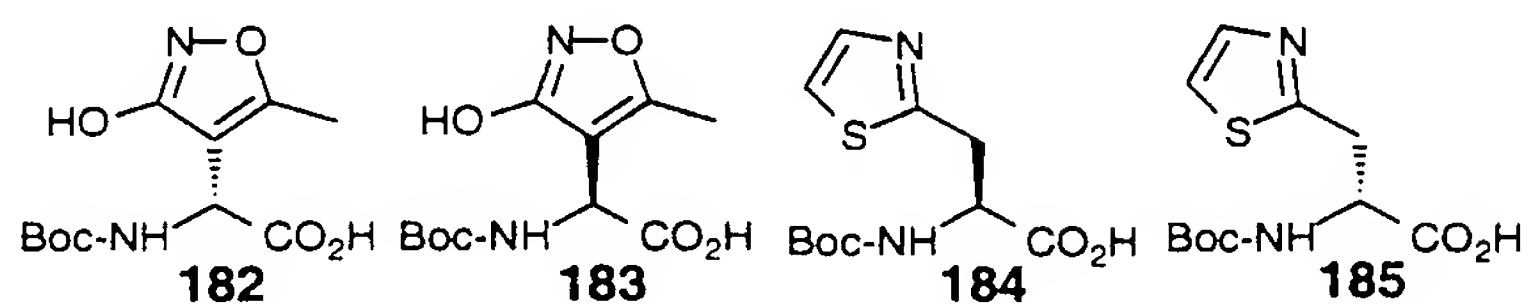
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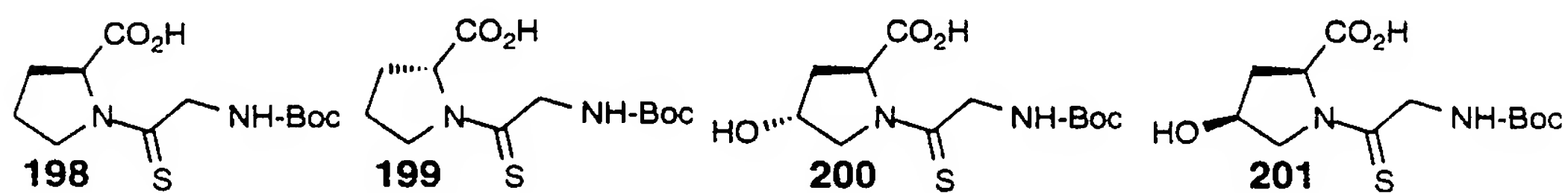
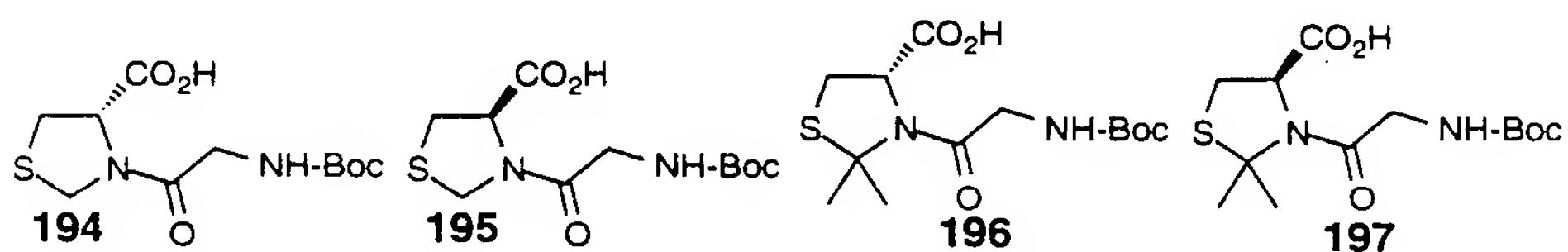
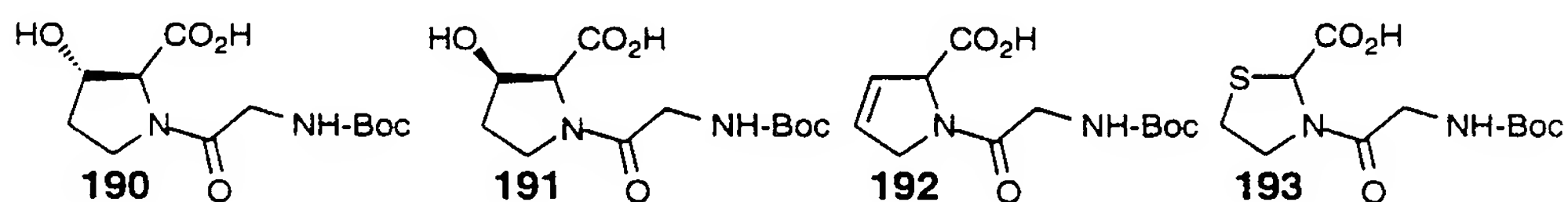




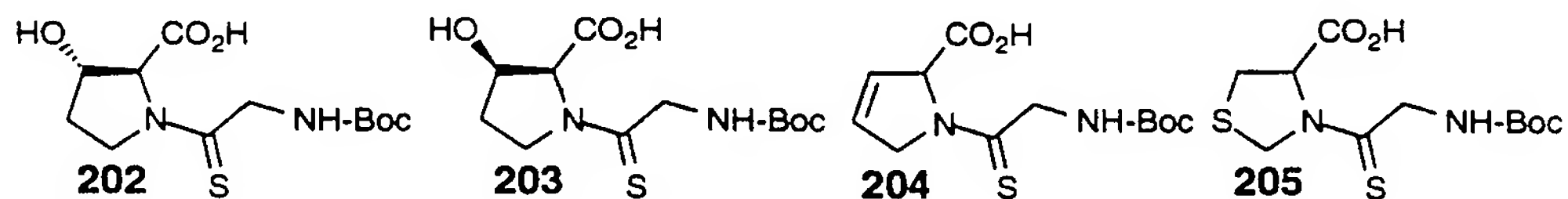
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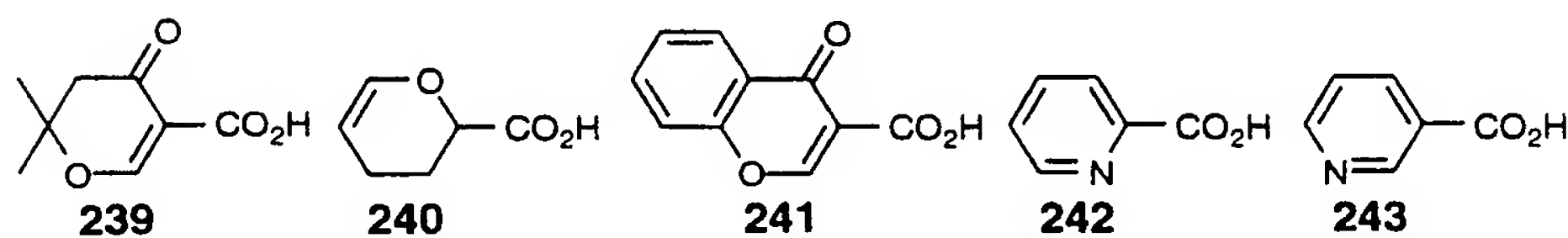
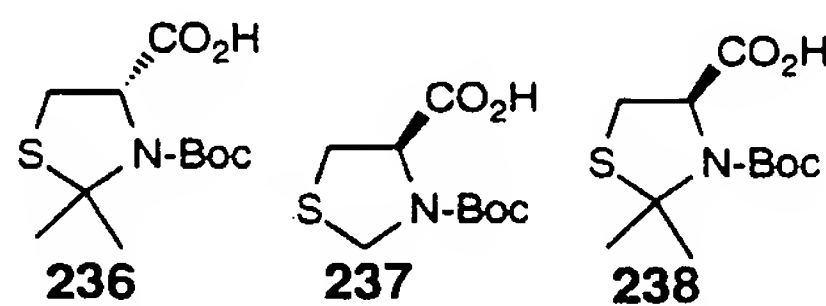
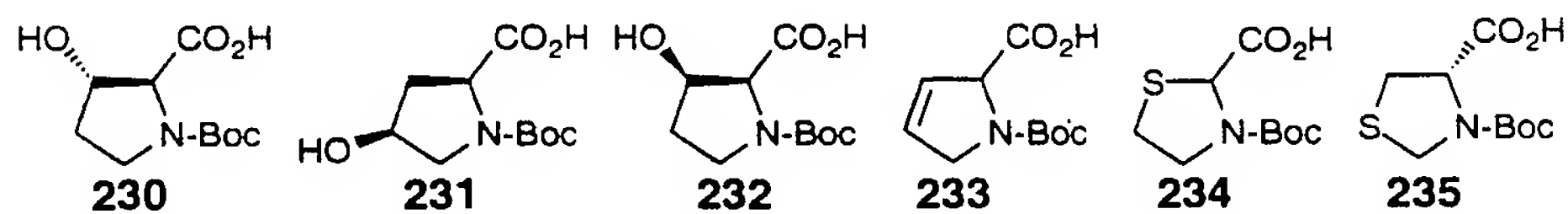
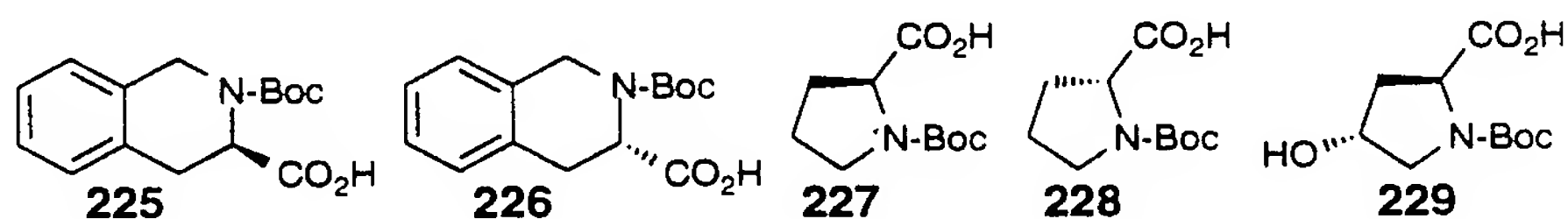
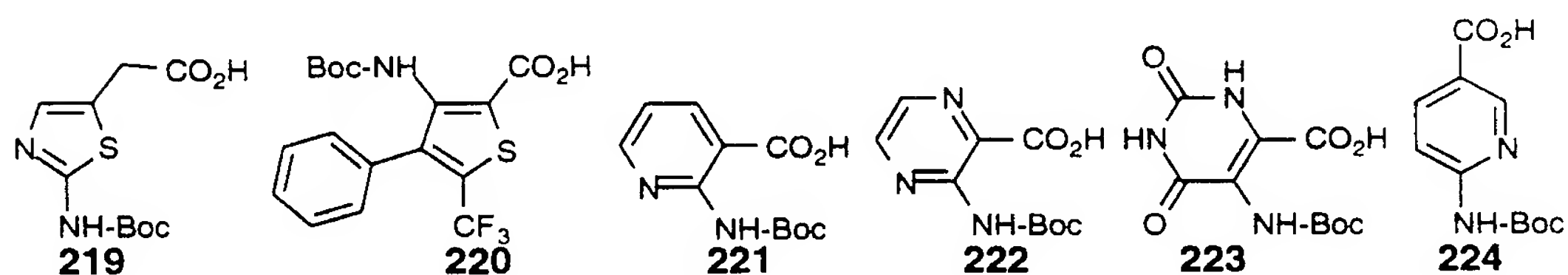
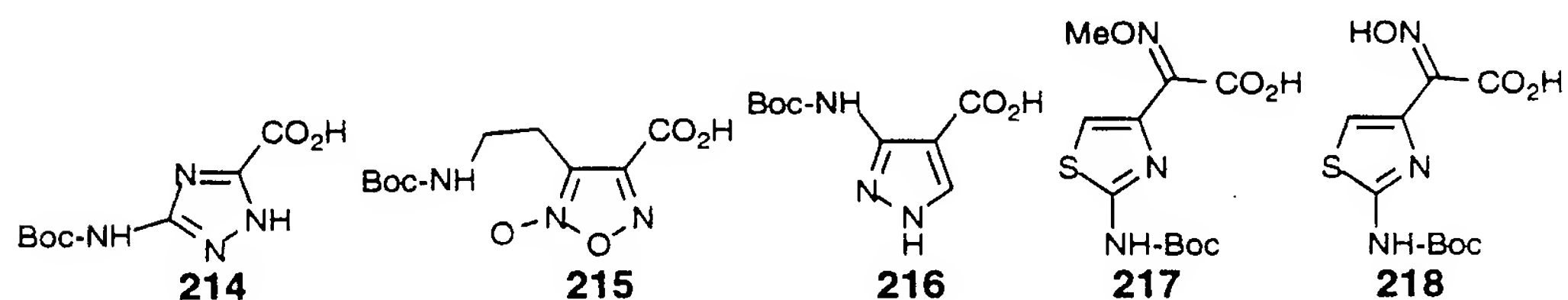
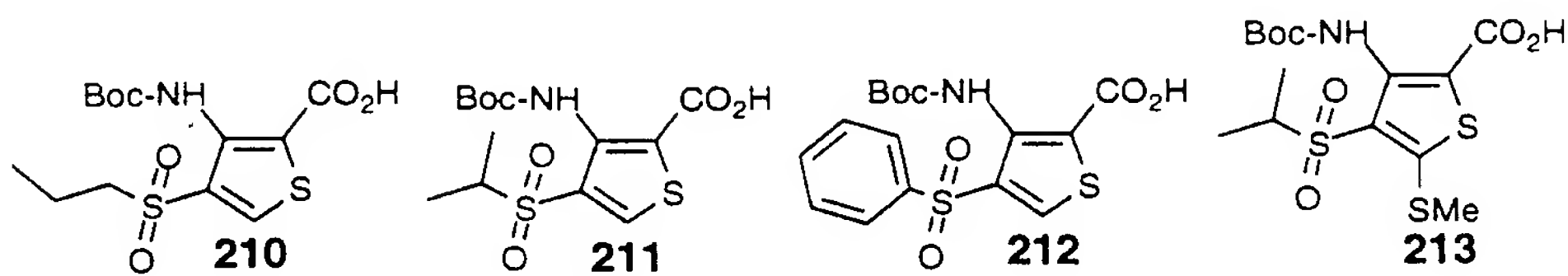
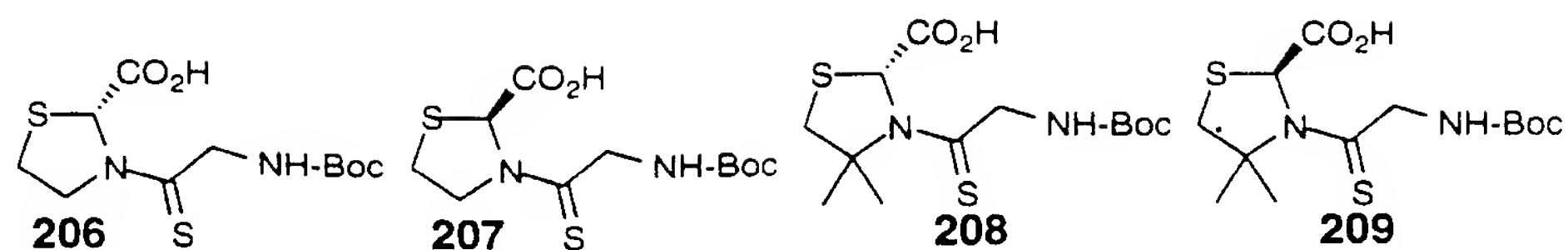
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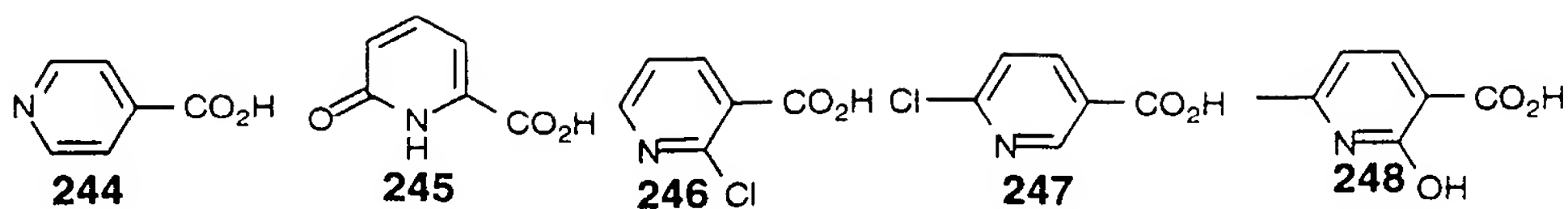


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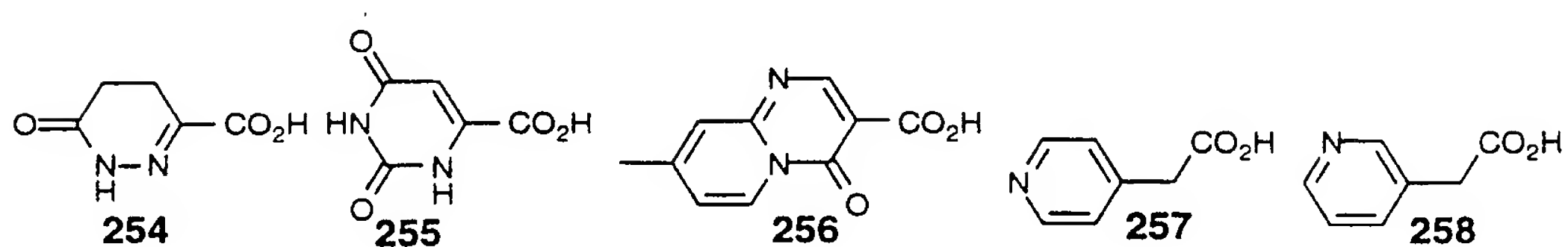
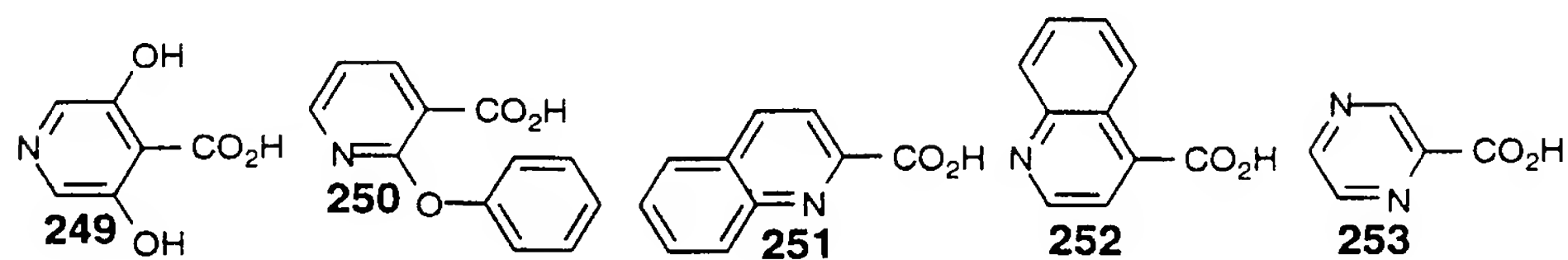




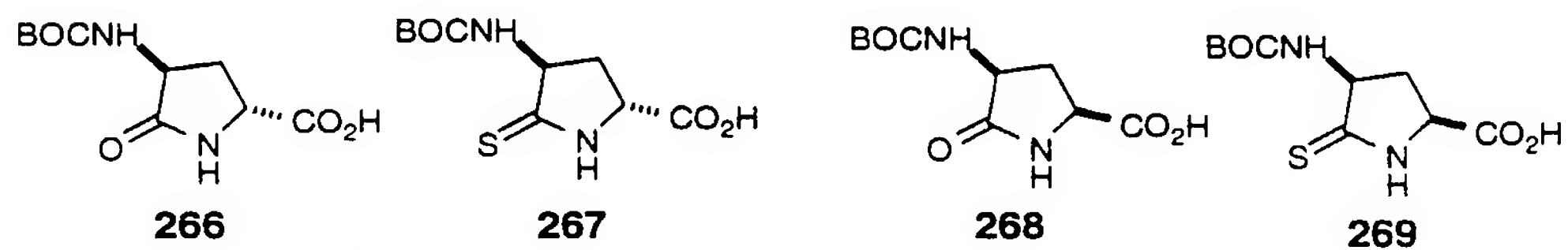
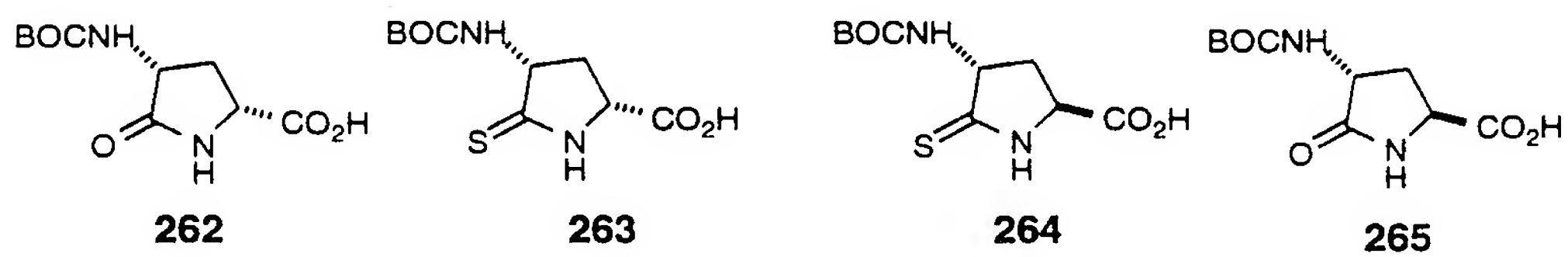
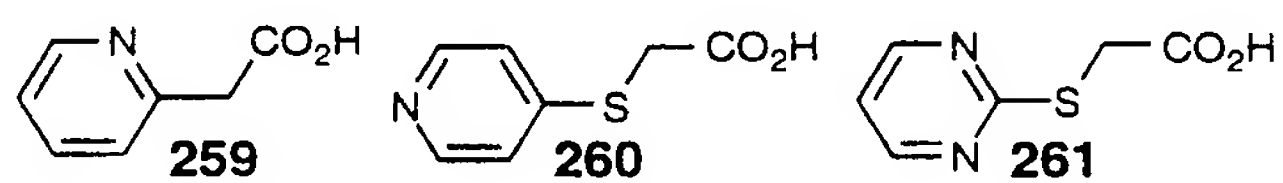




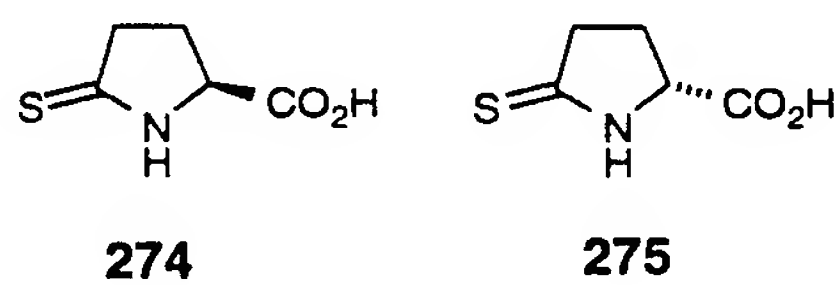
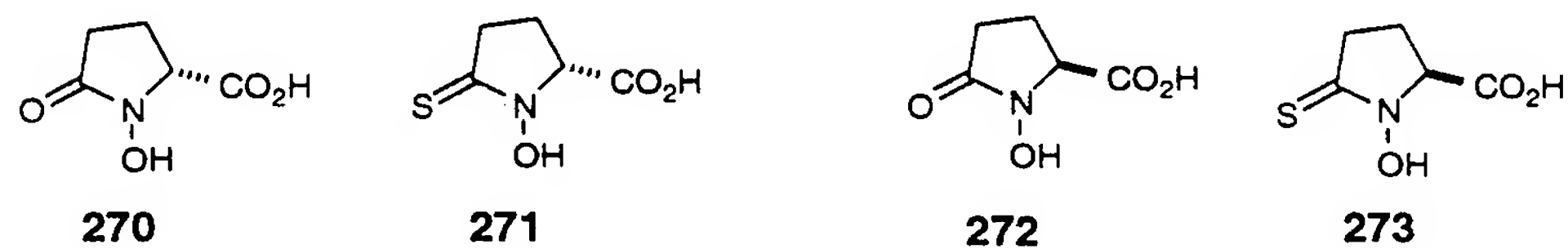
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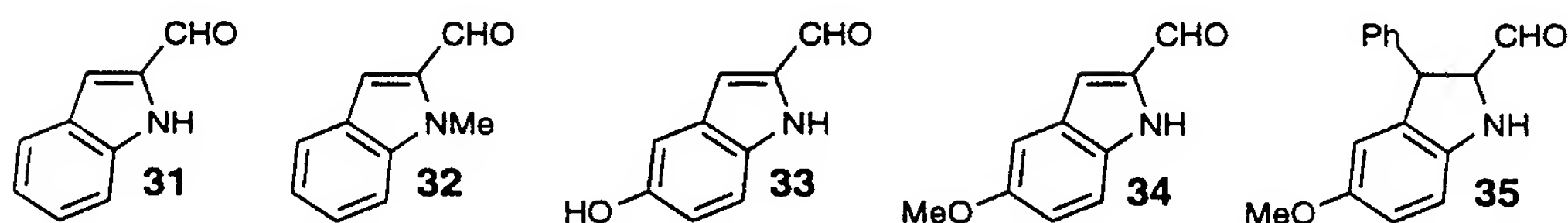
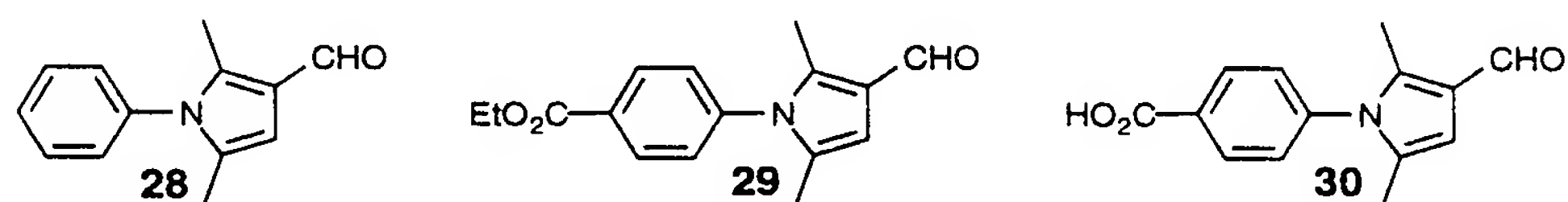
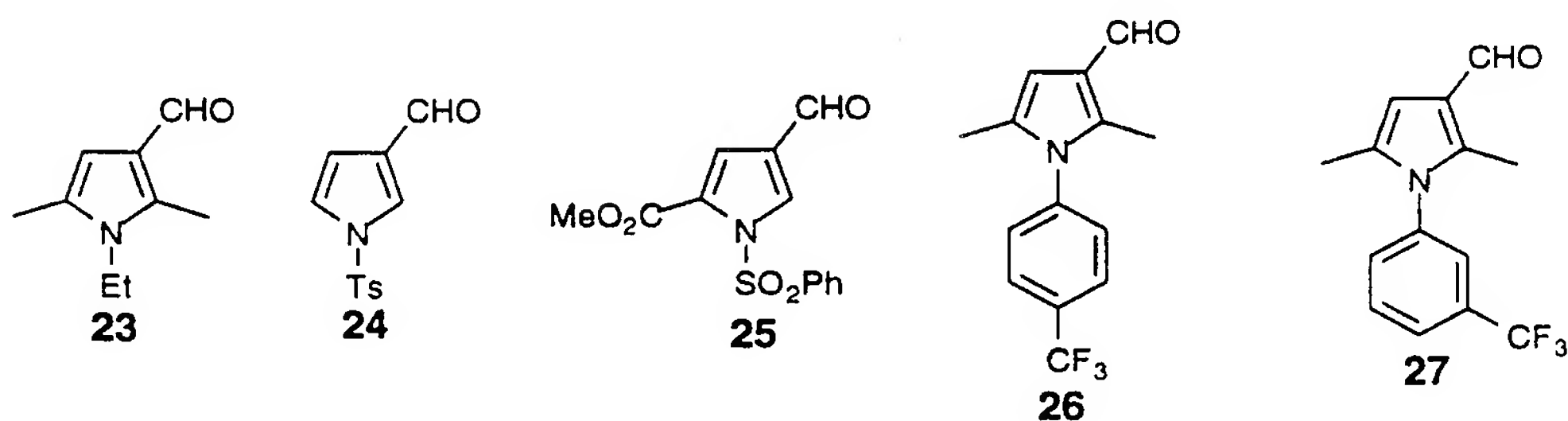
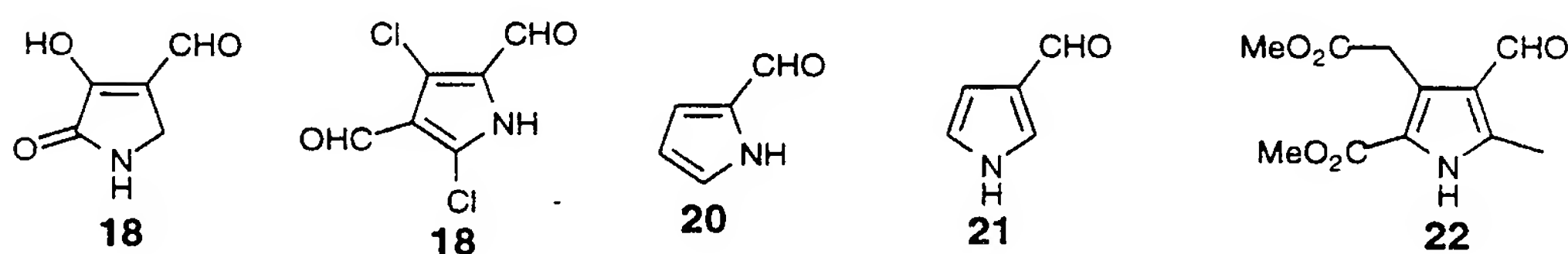
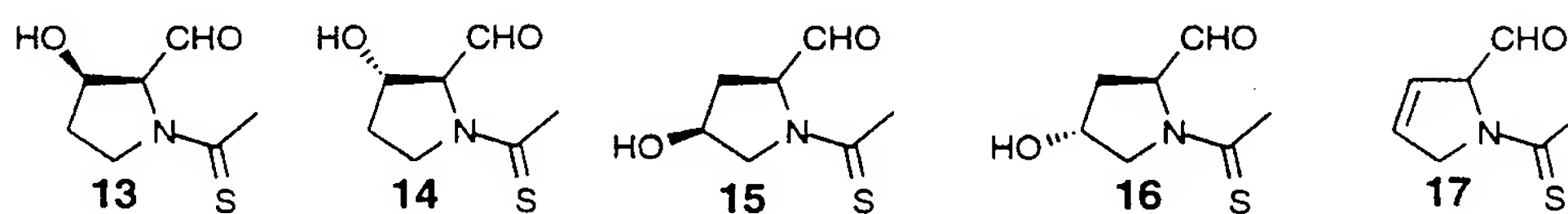
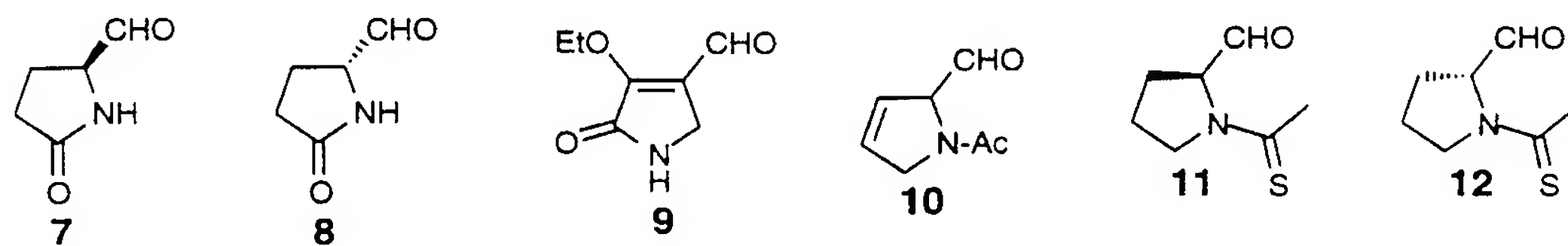
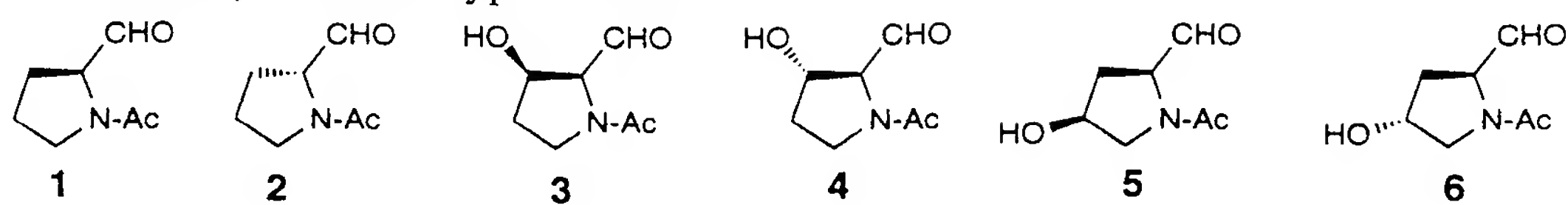
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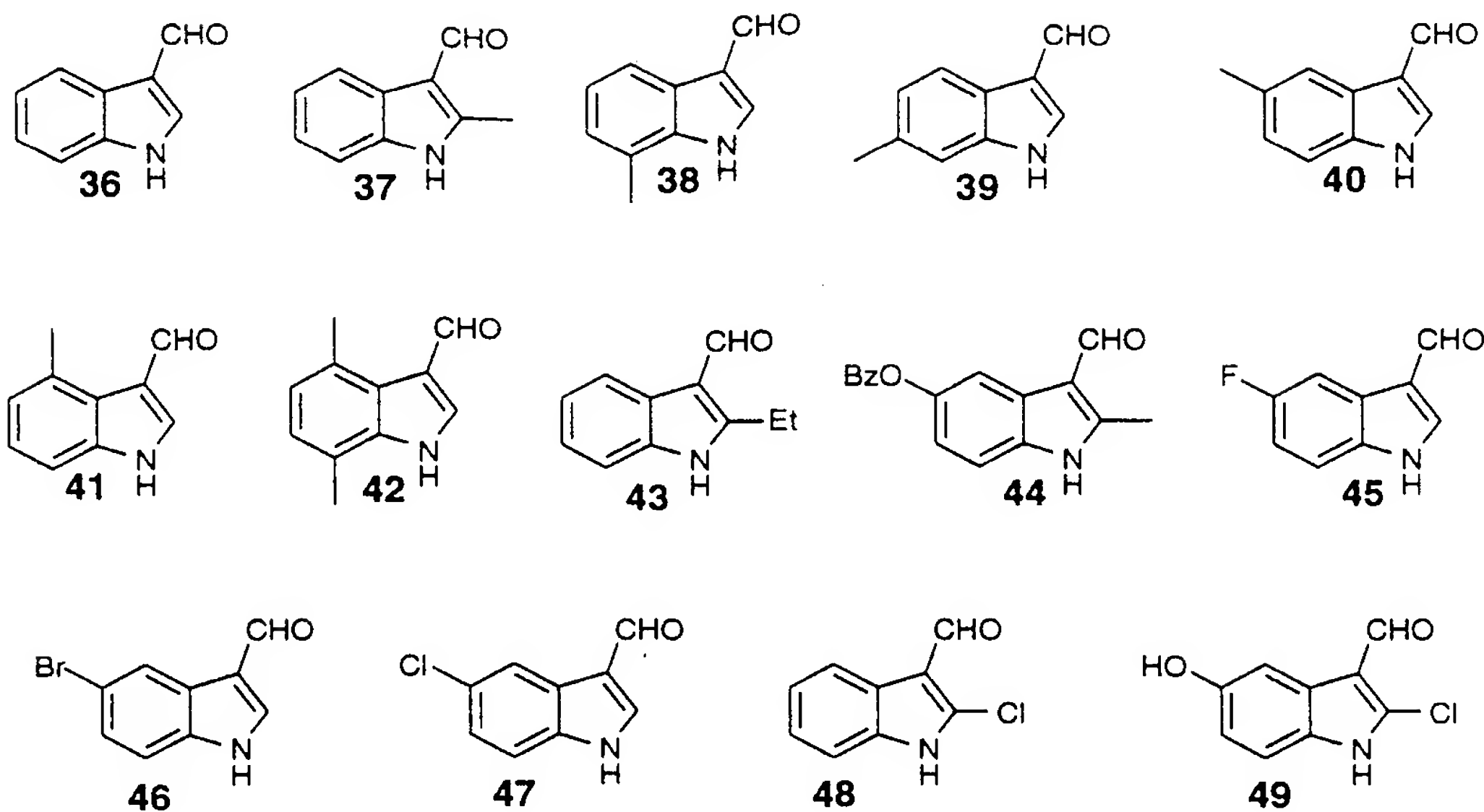
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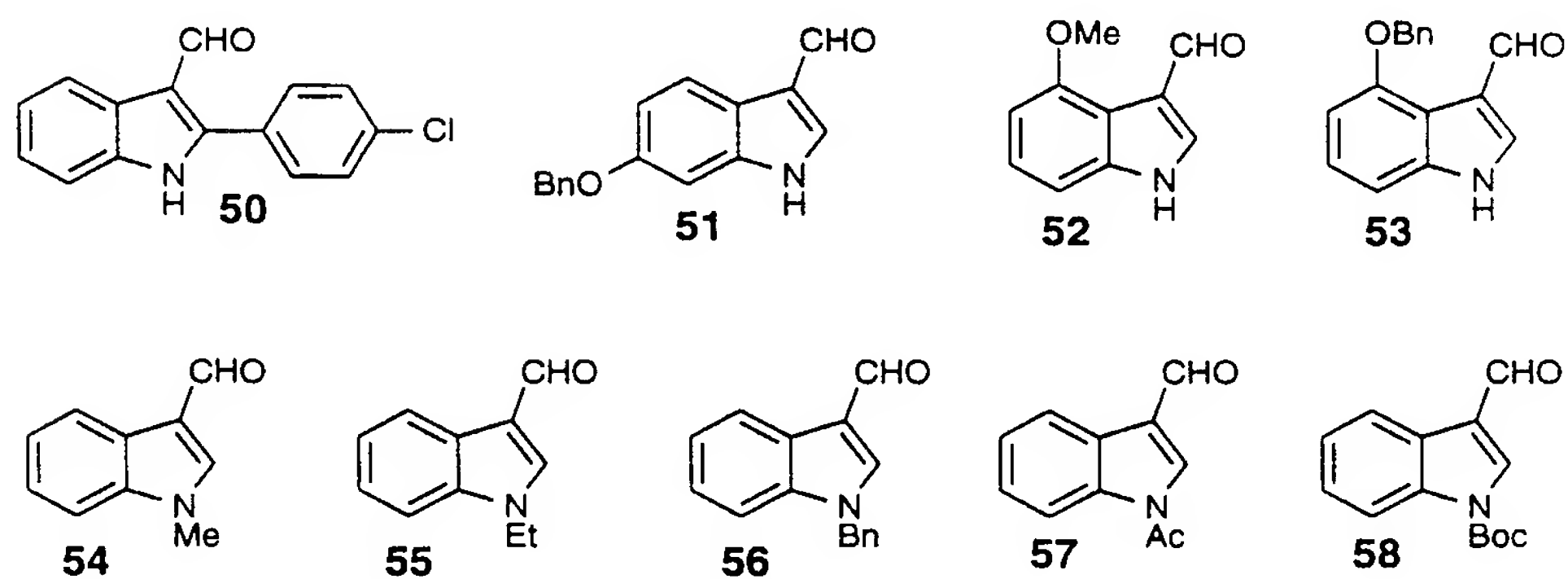
2830 Table 14. Aldehydes of the type A-CHO



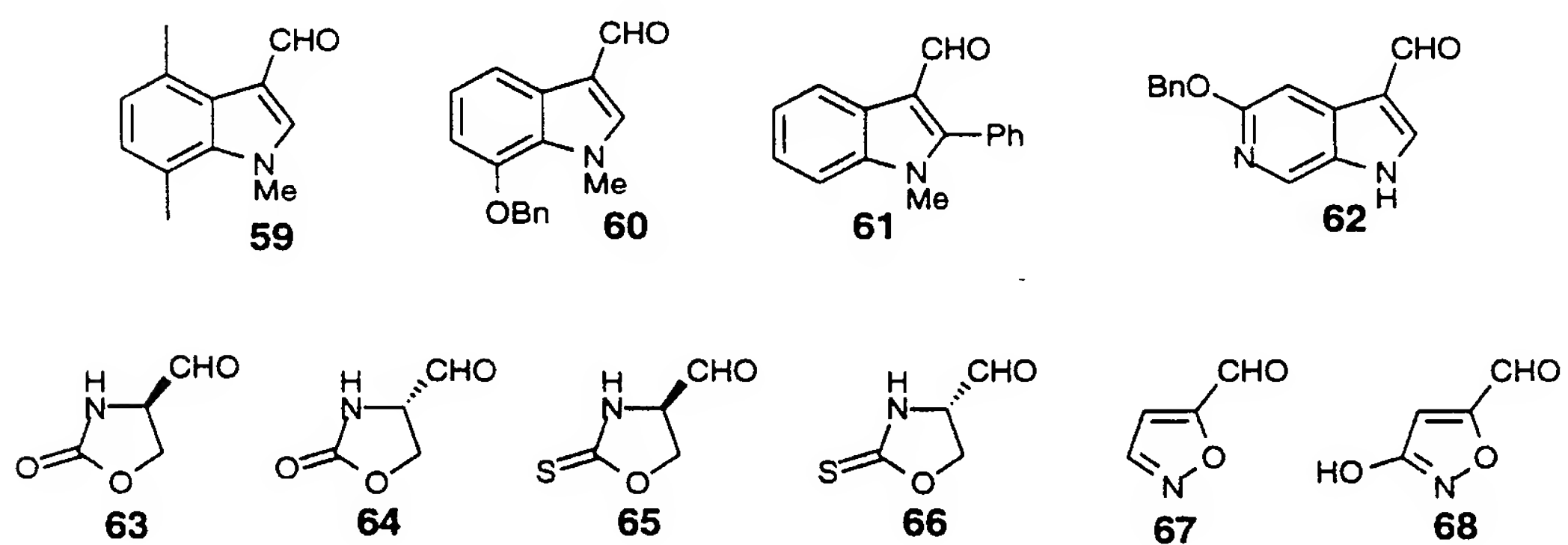
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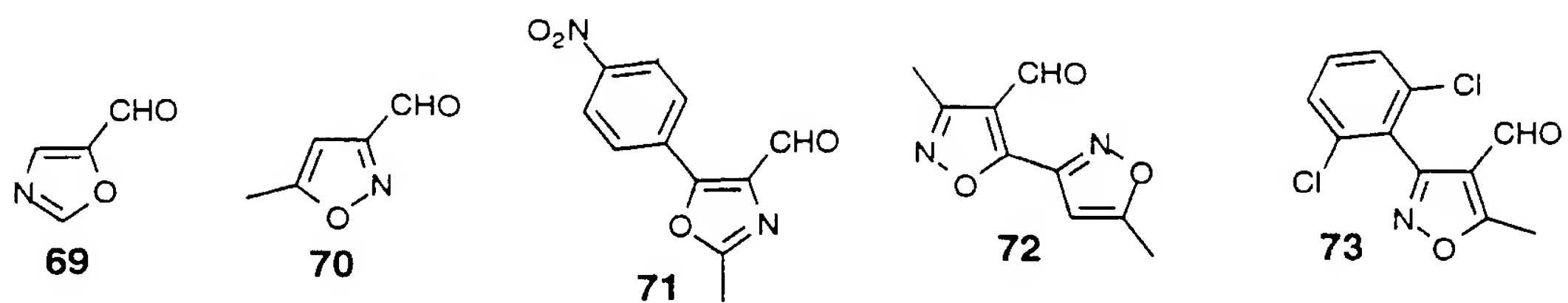


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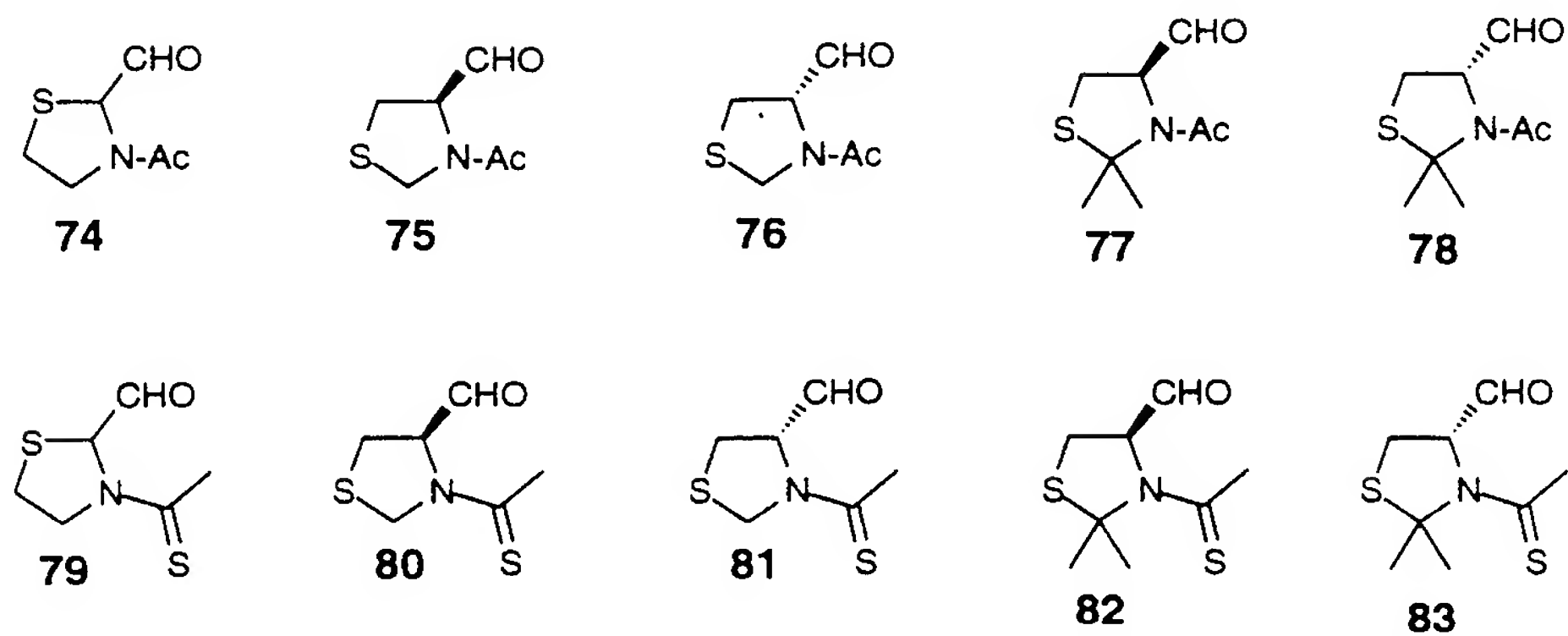


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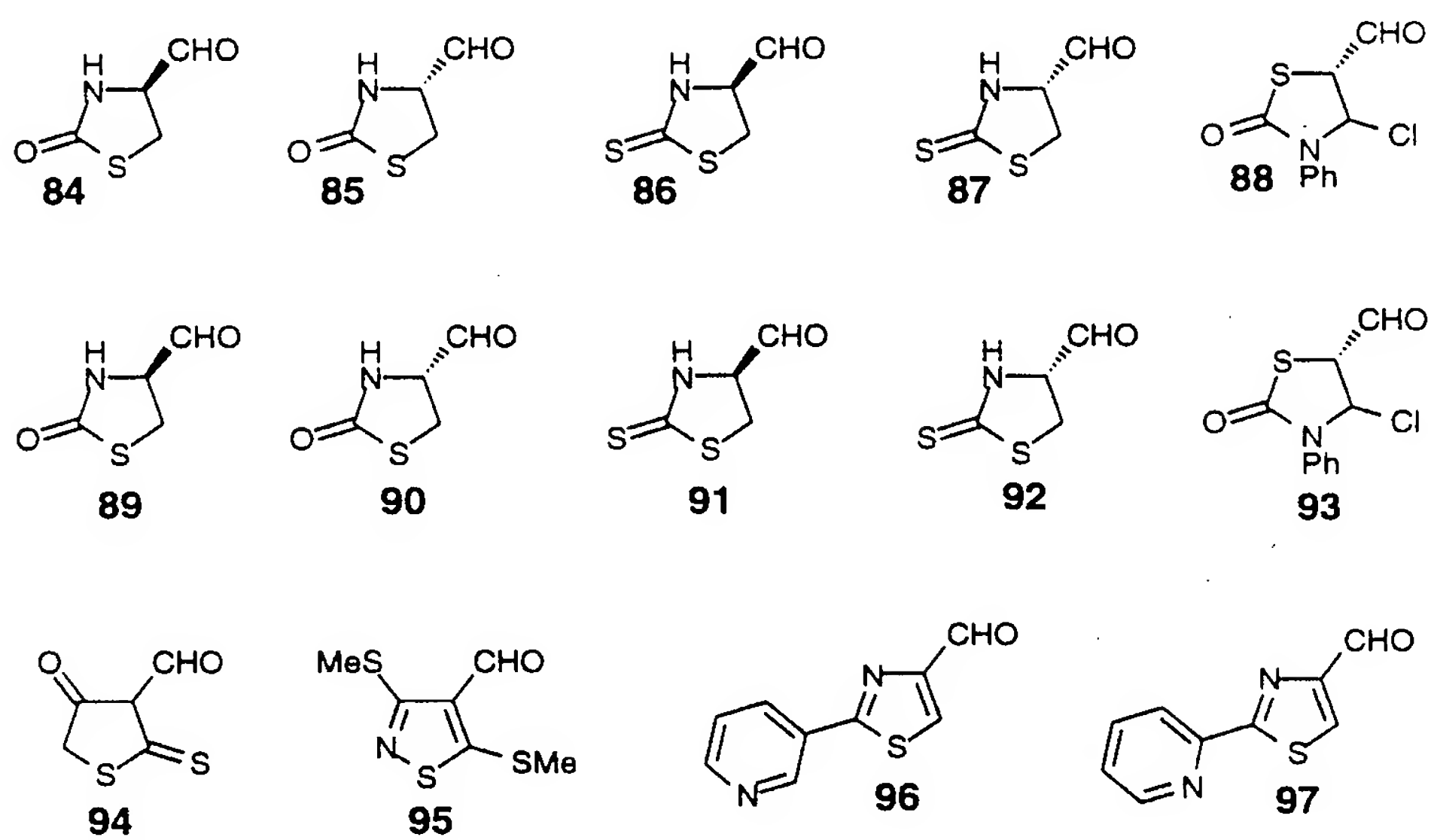




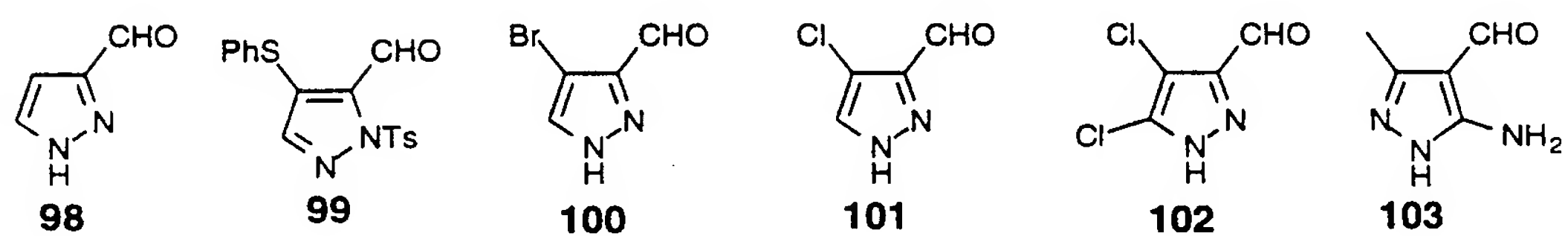
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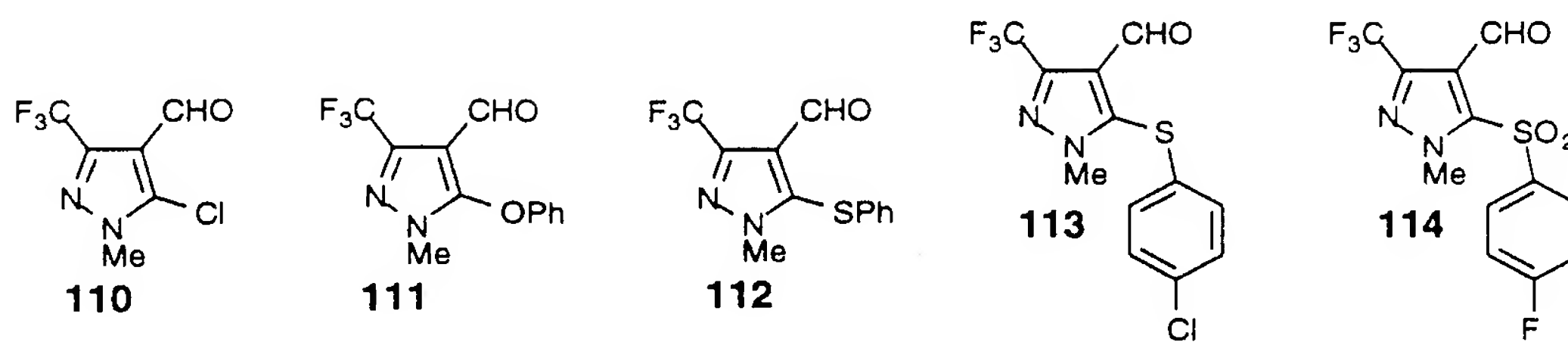
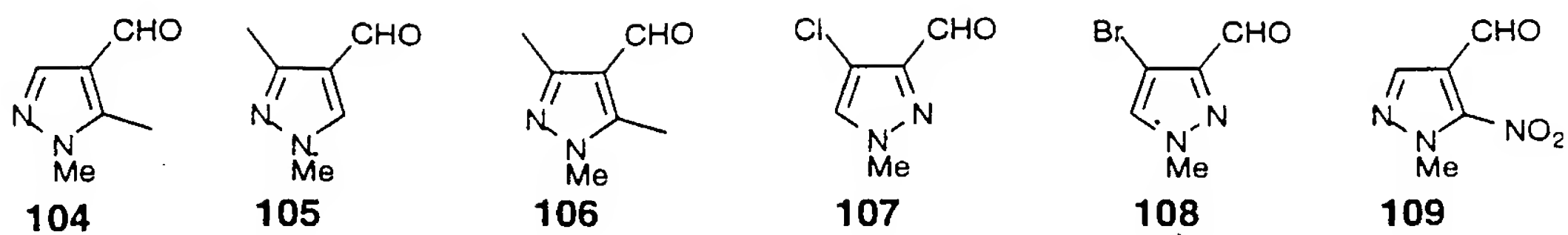


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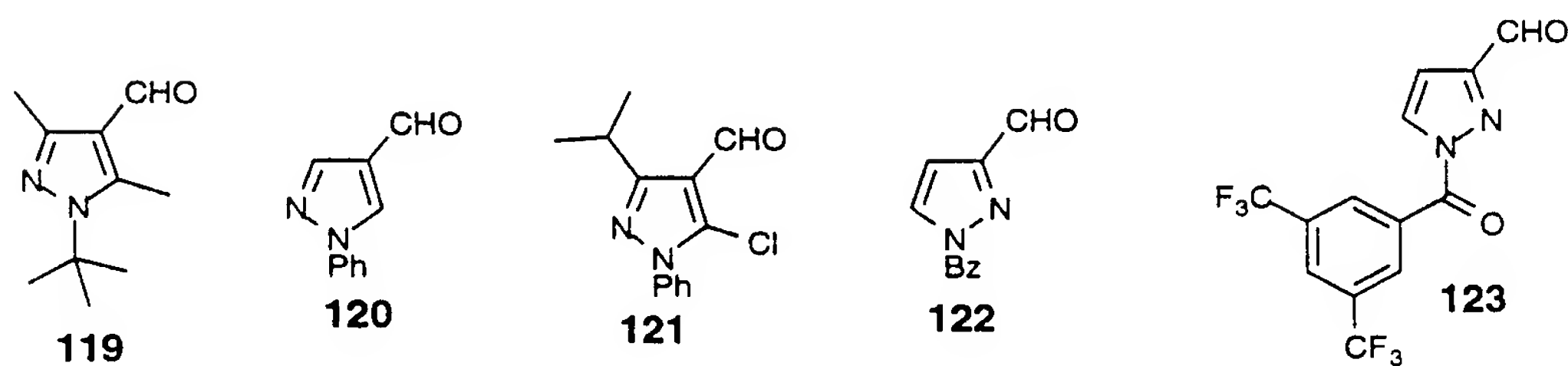
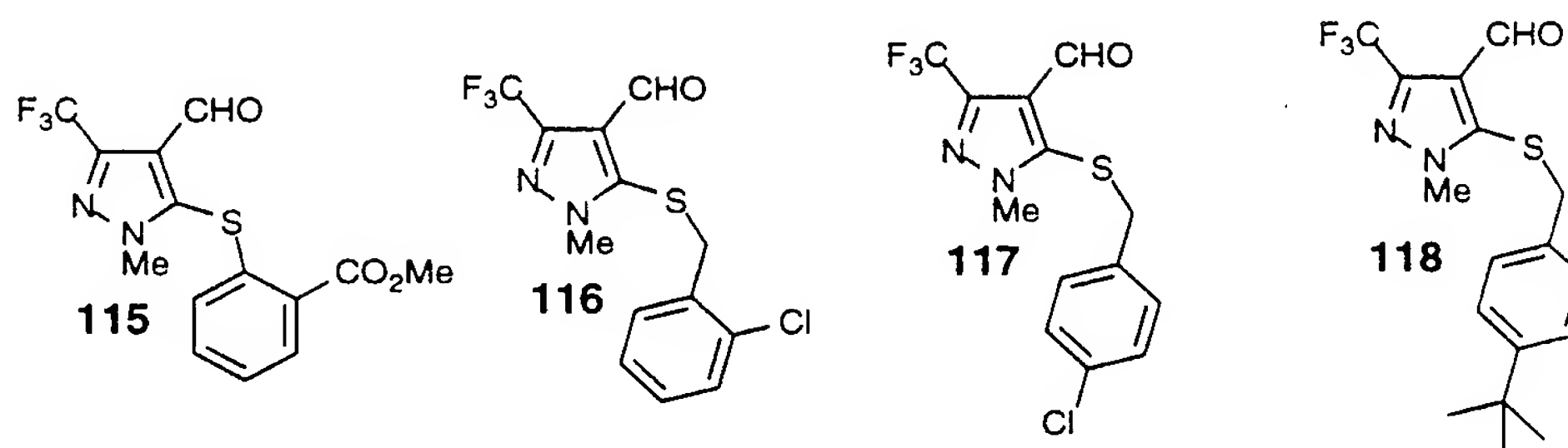


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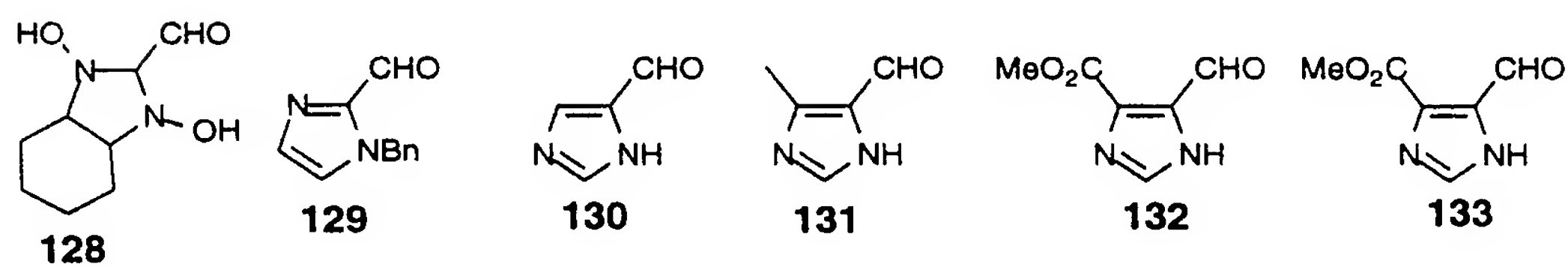
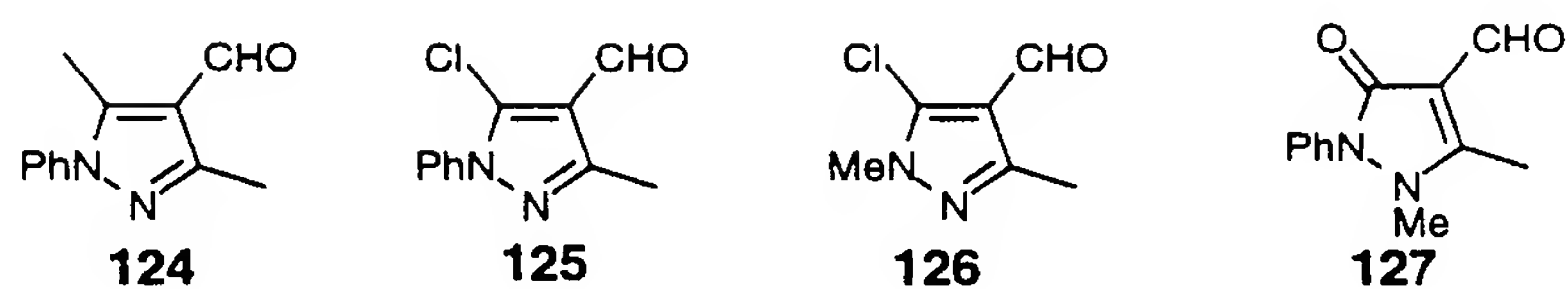




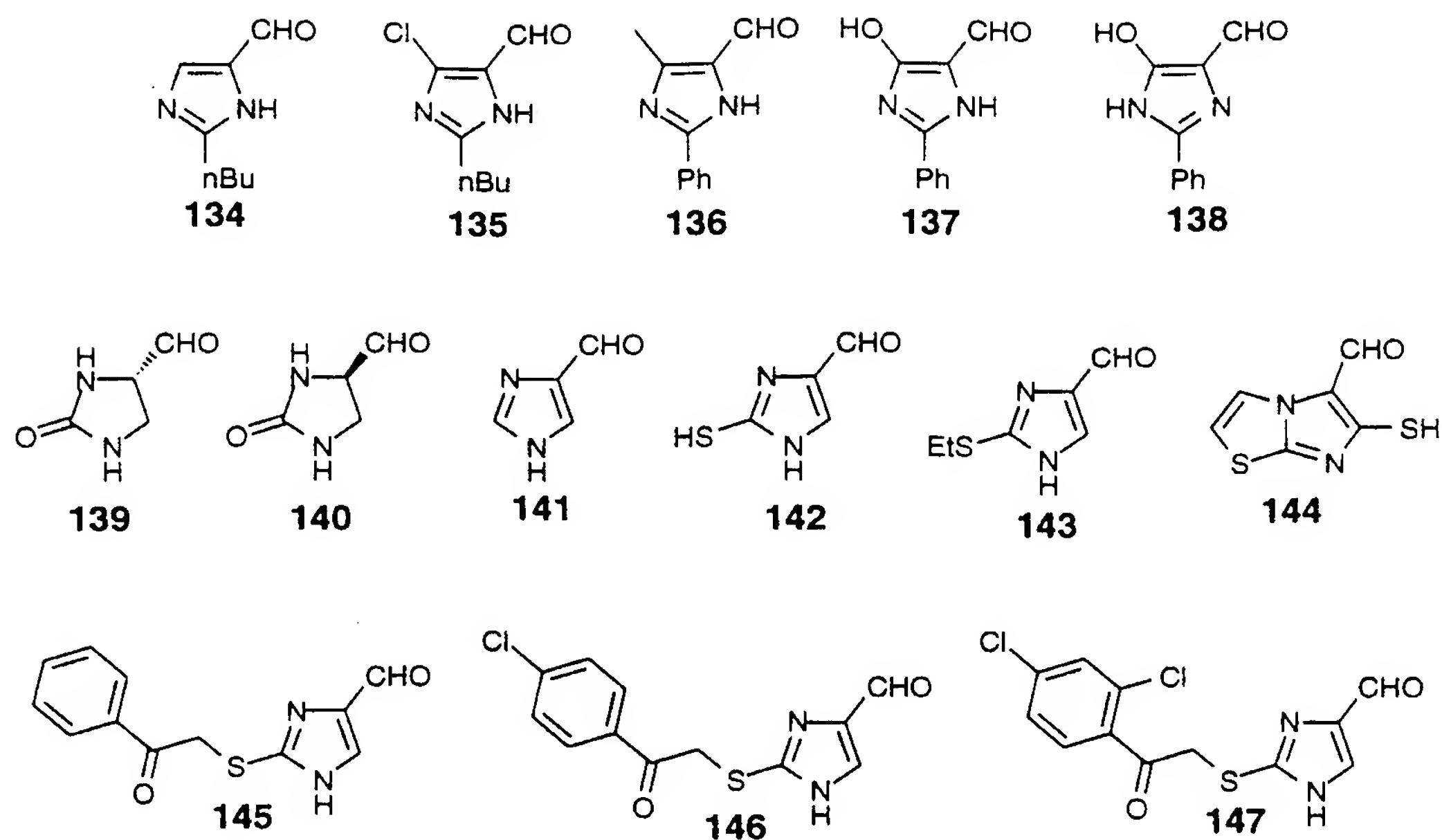
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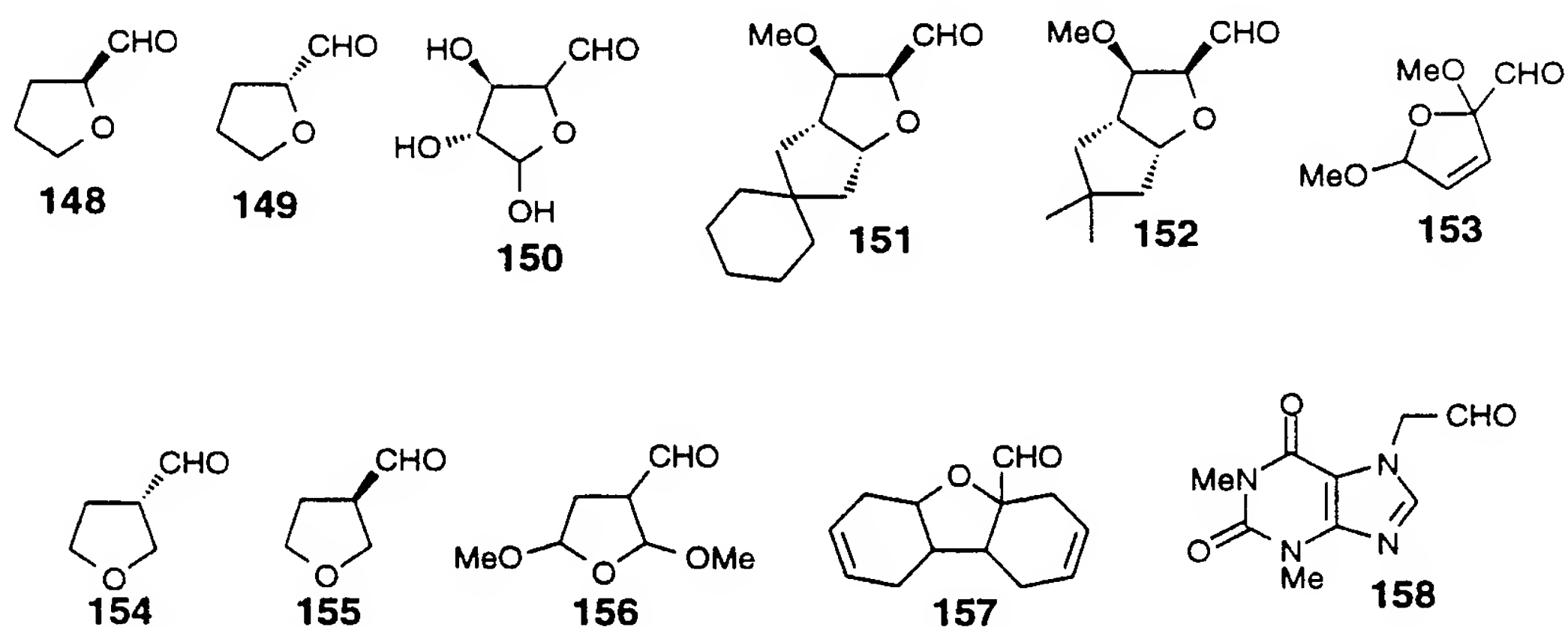
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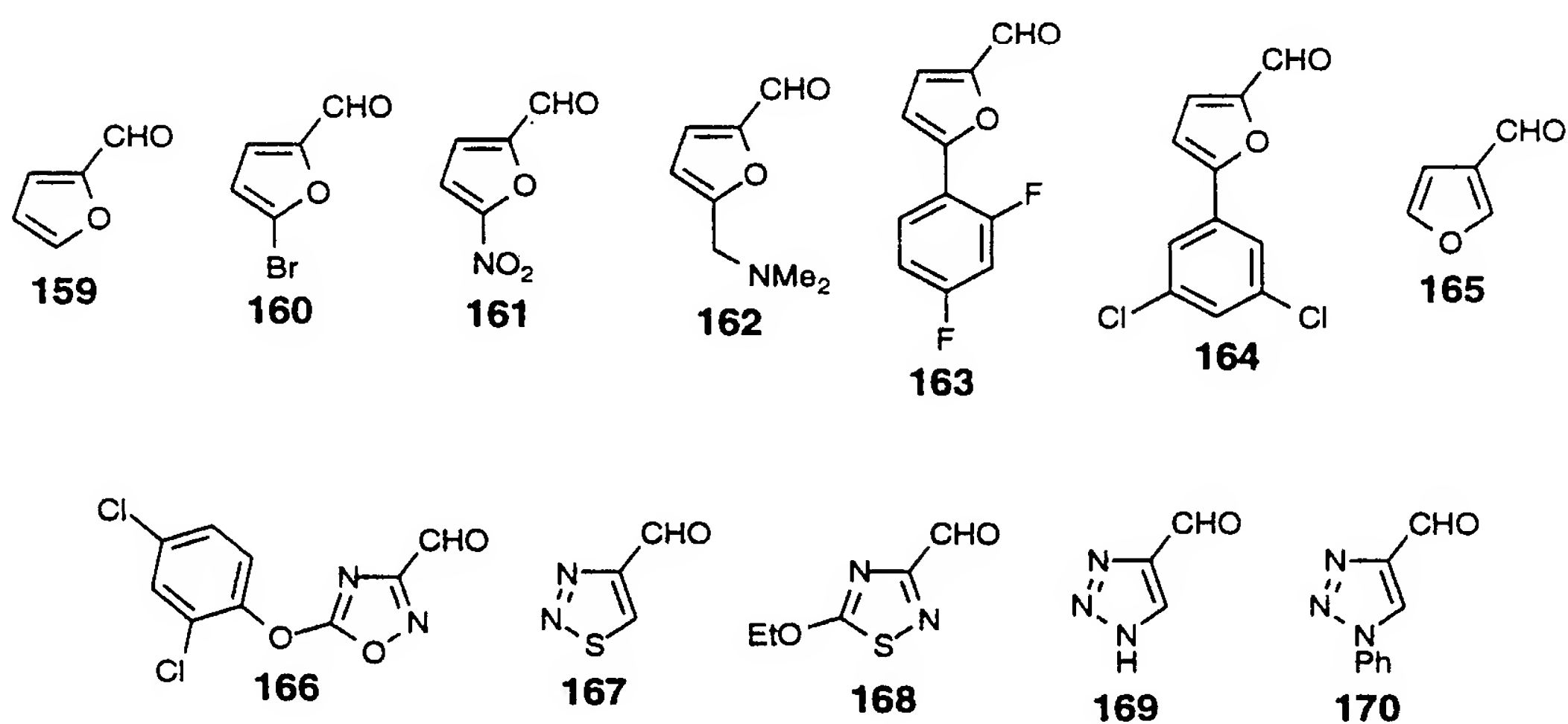
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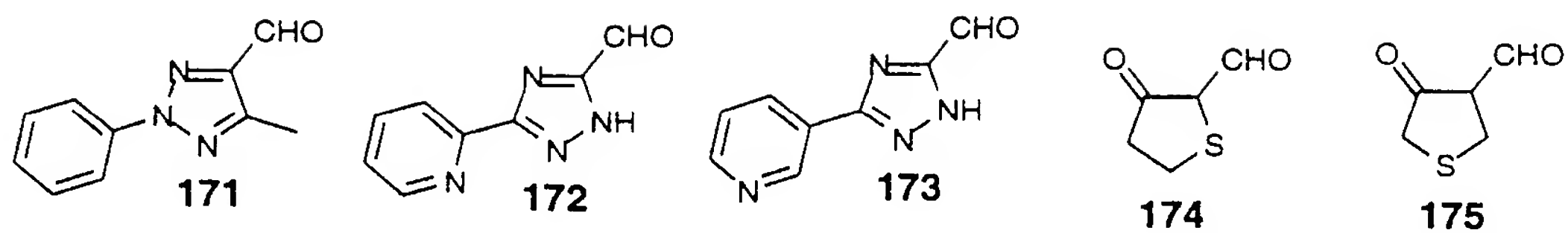


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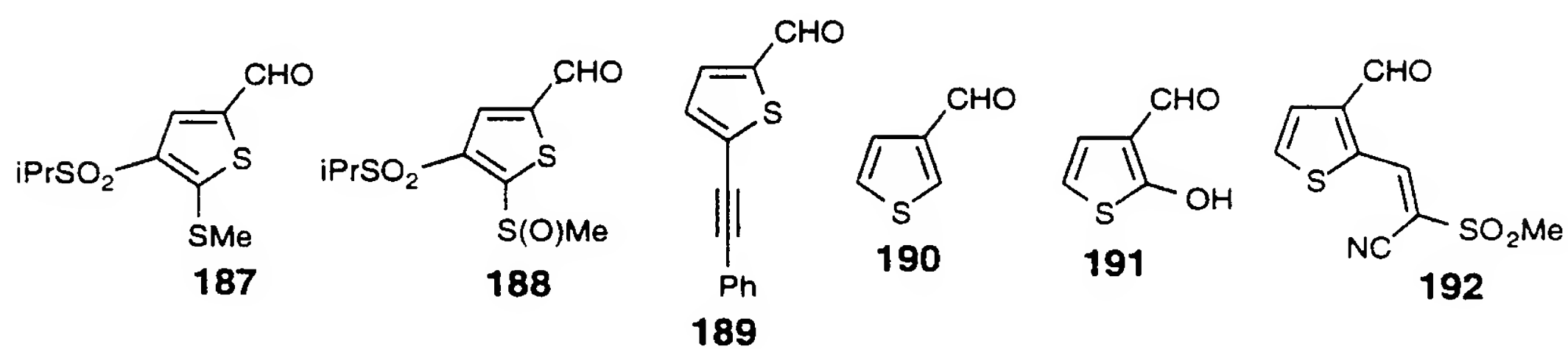
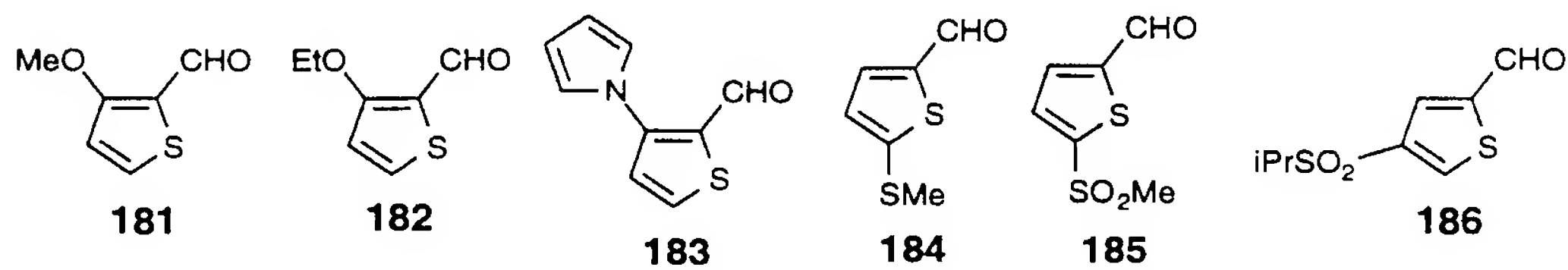
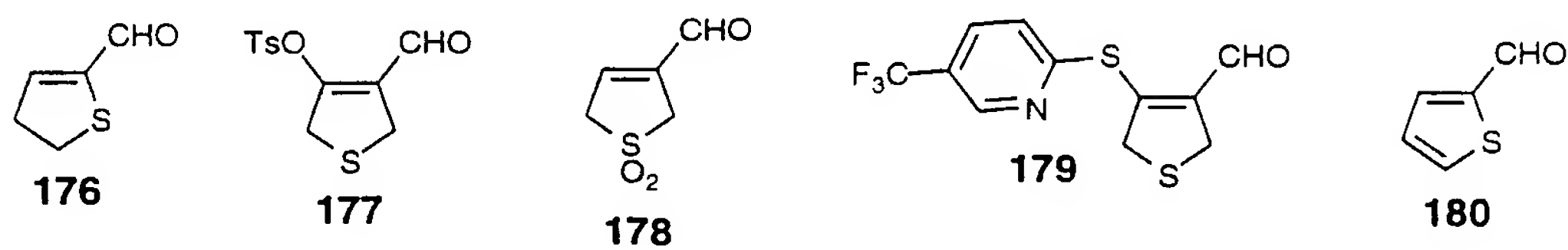


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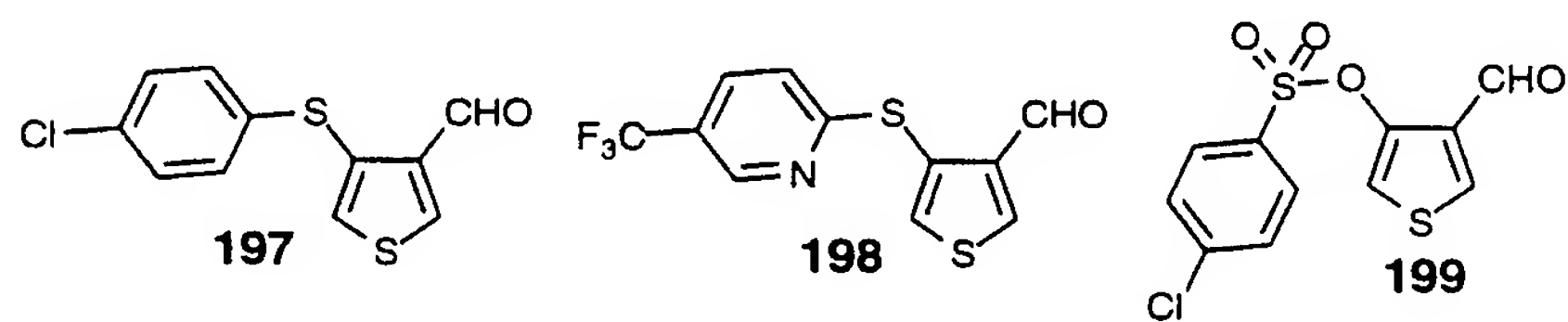
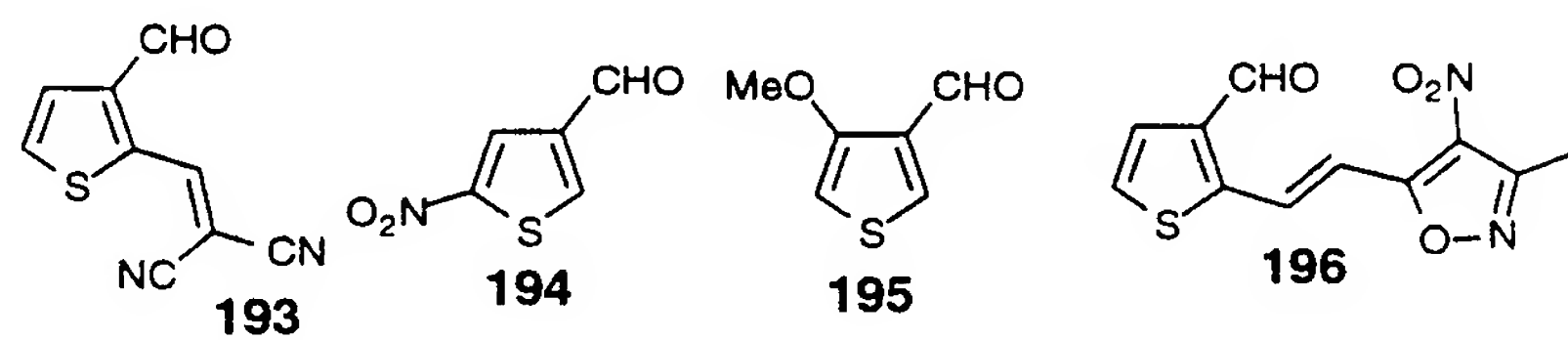




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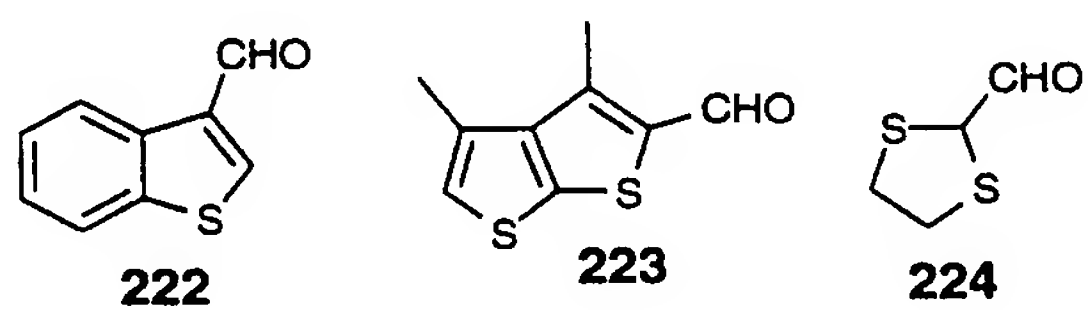
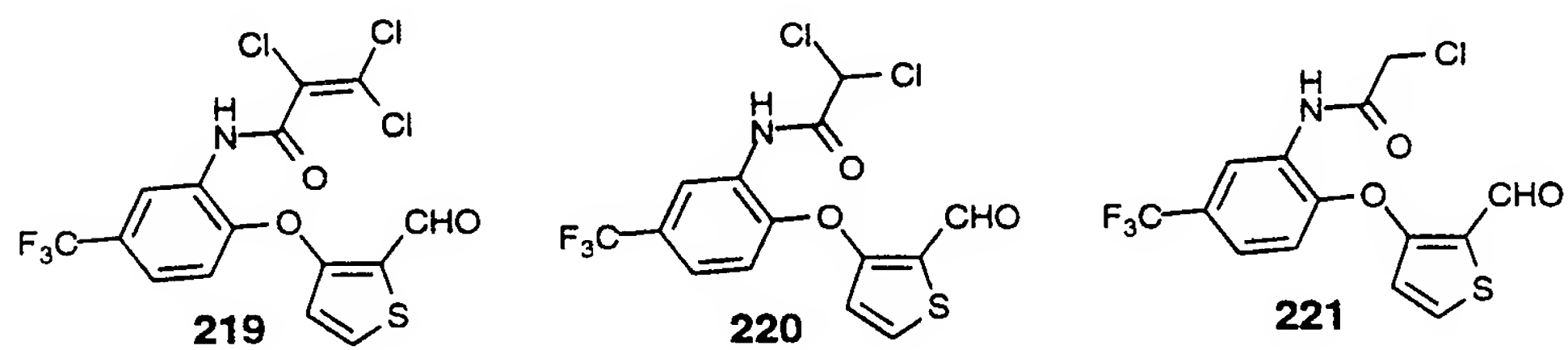
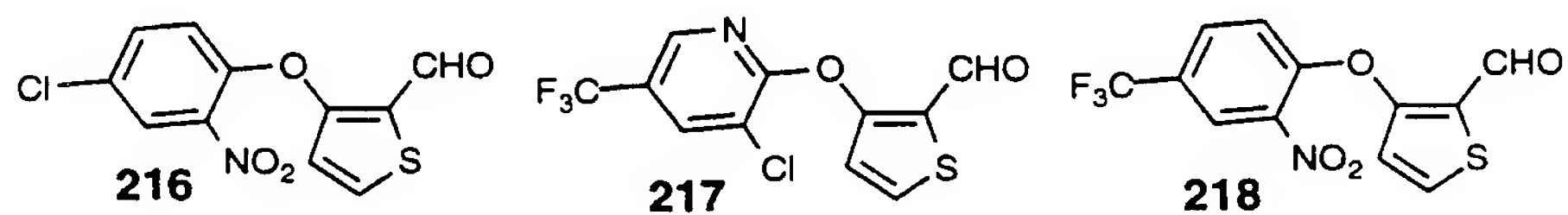
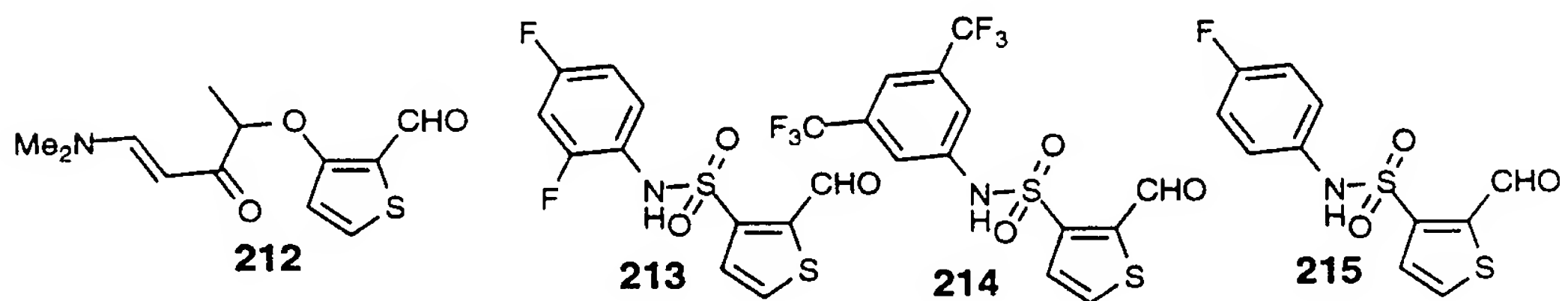
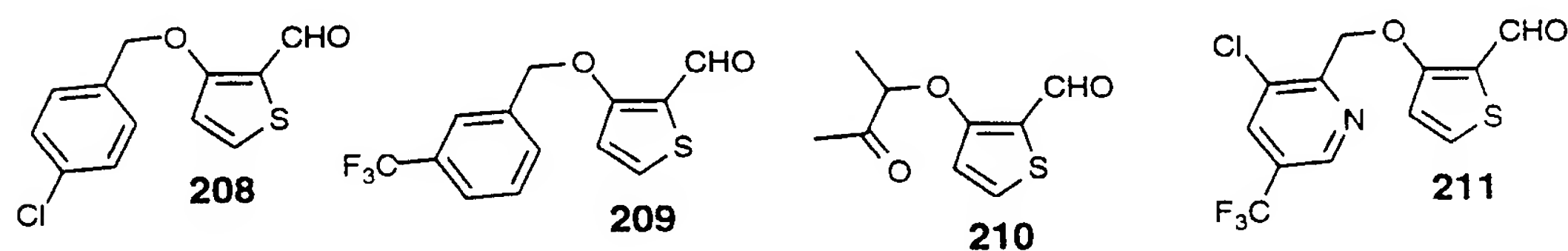
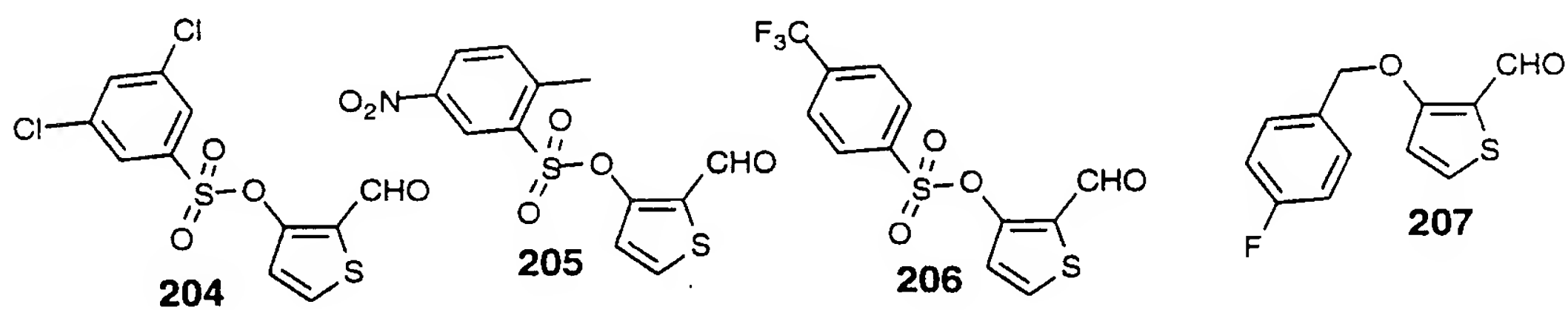
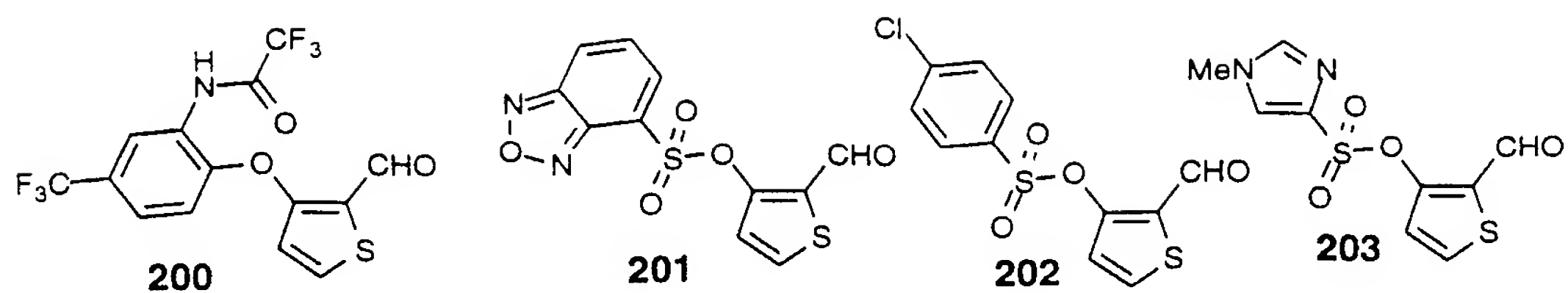


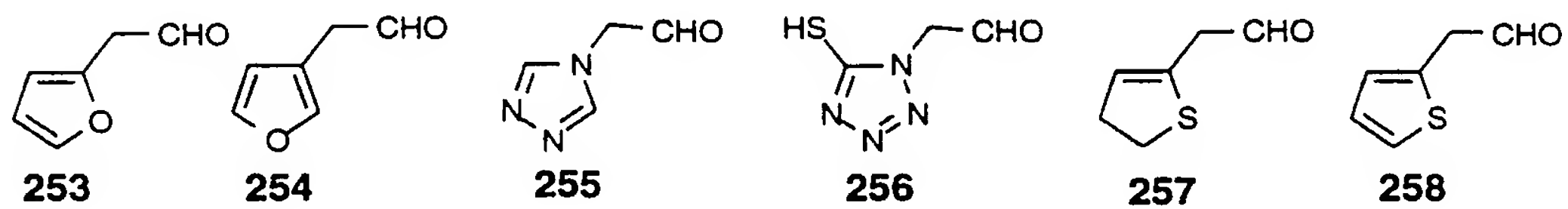
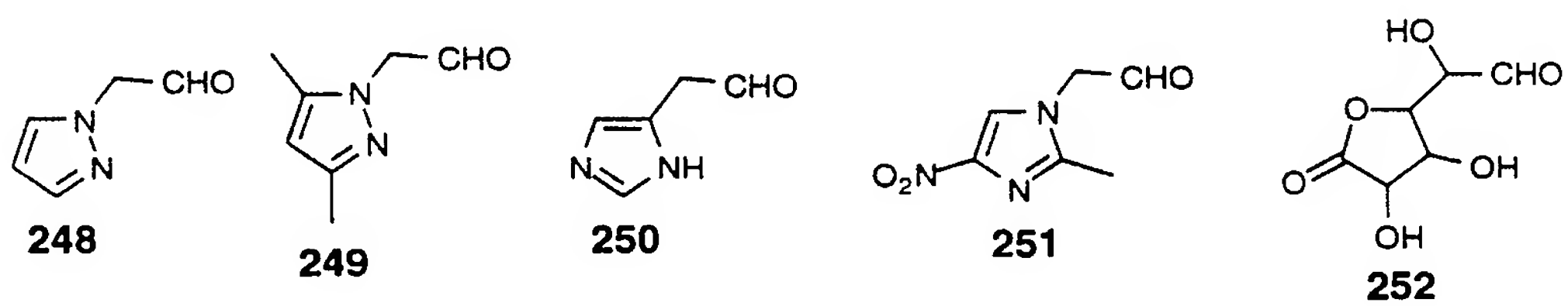
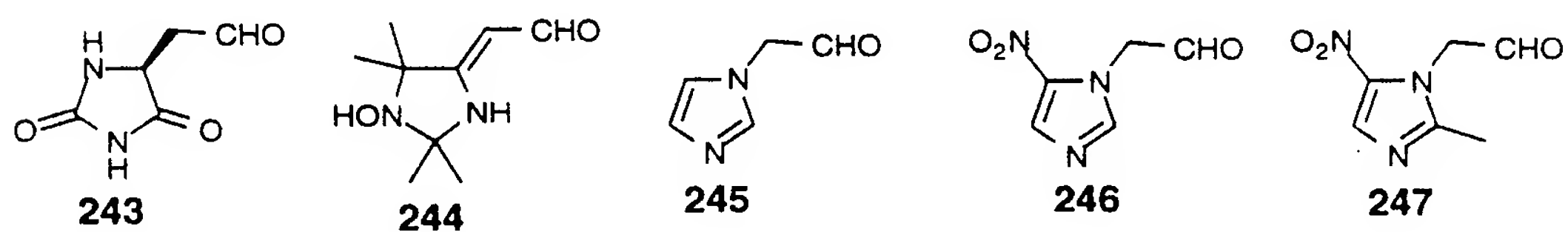
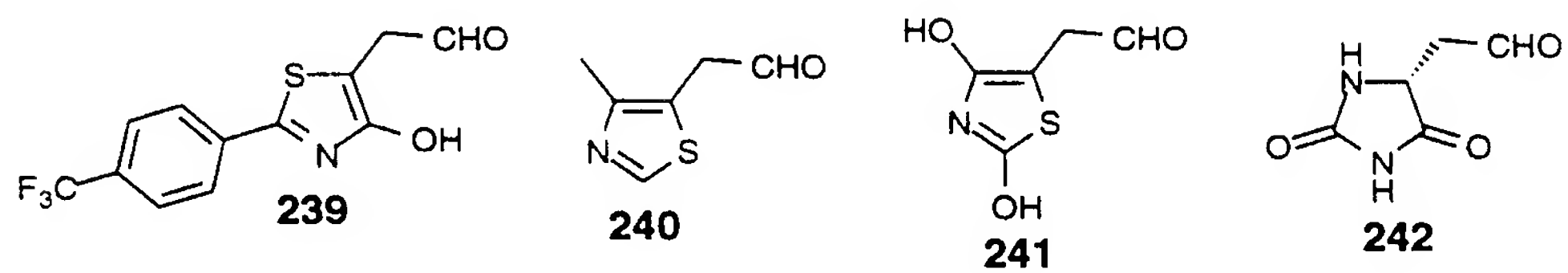
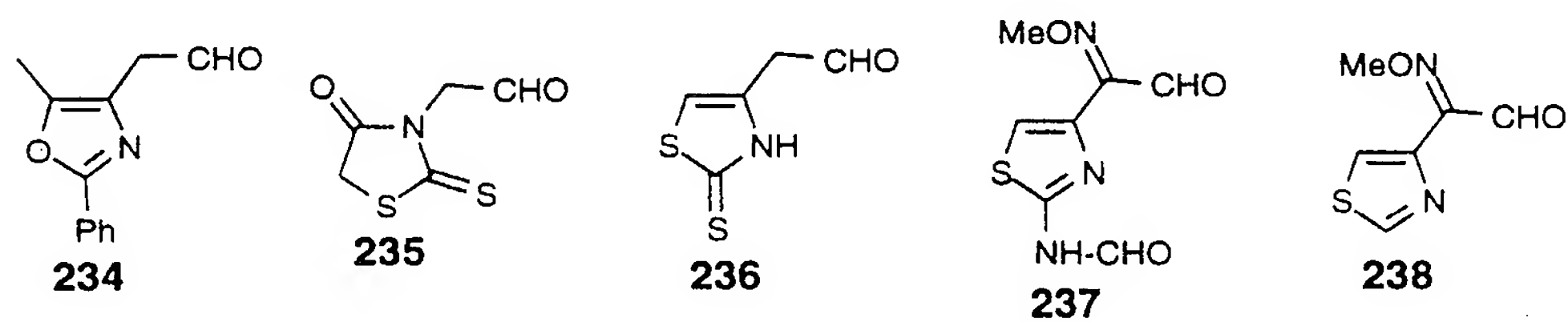
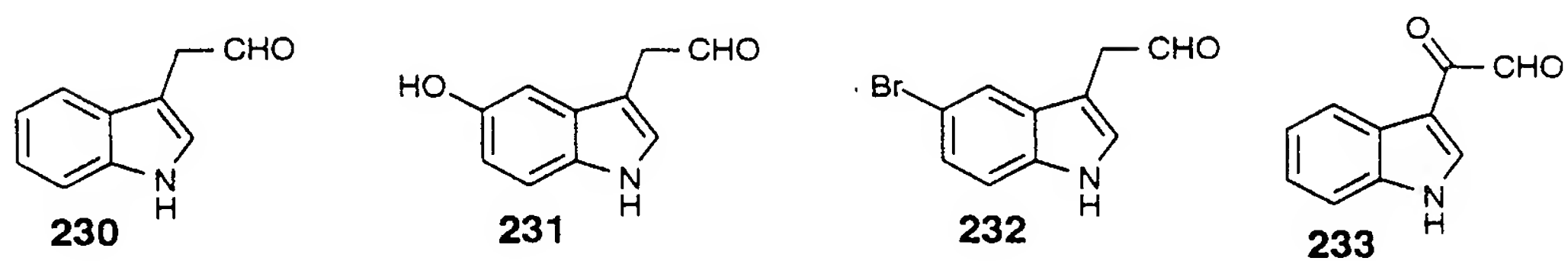
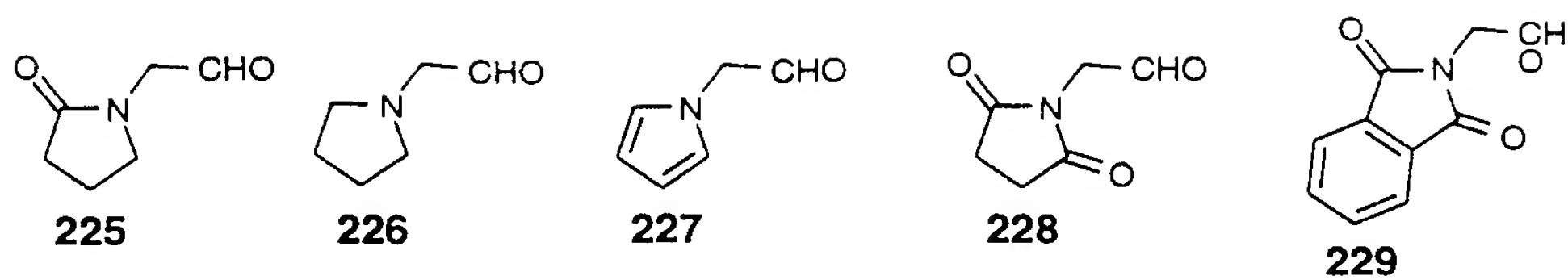
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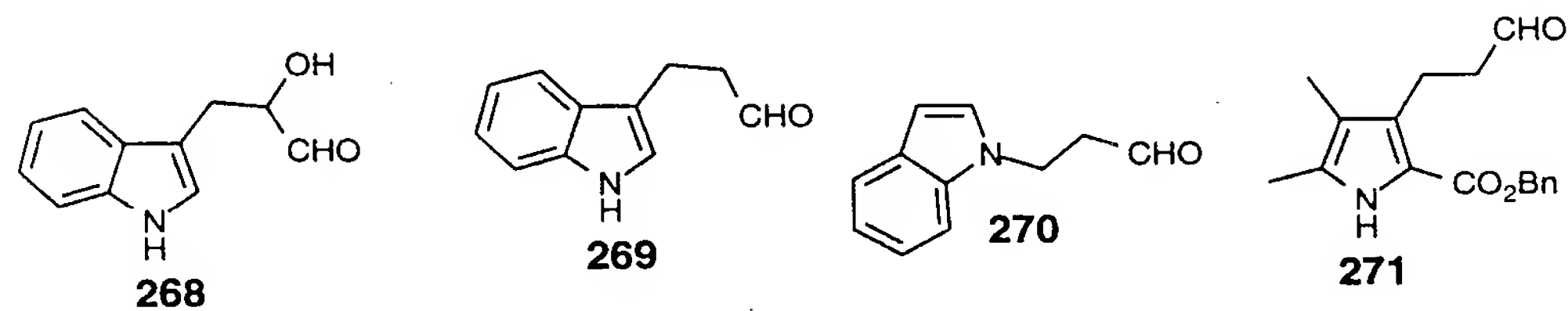
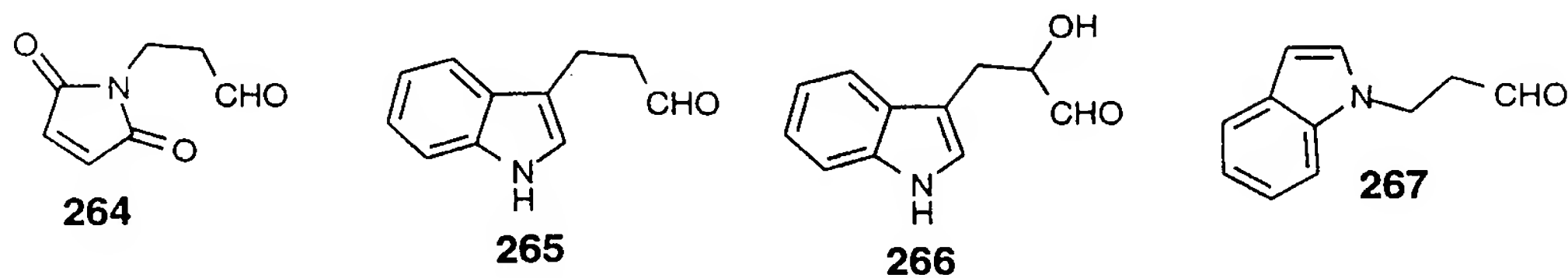
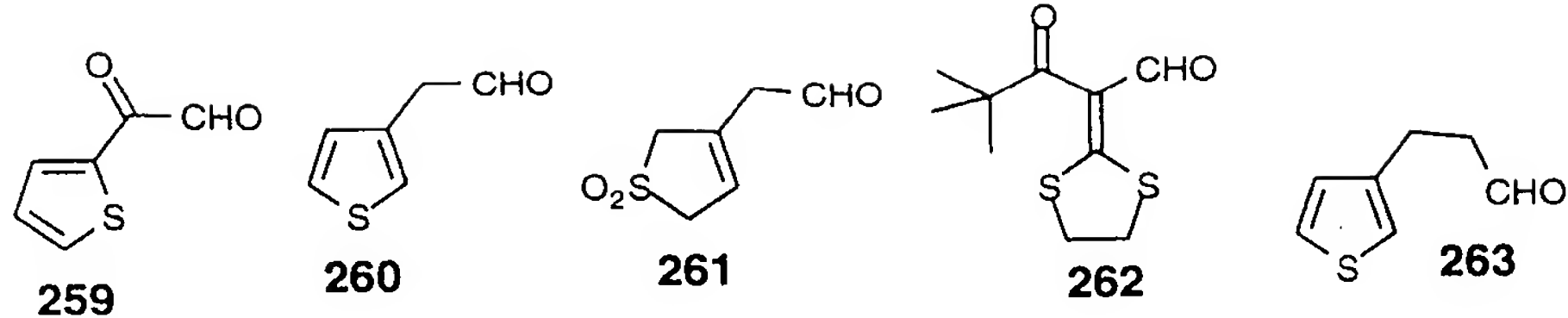
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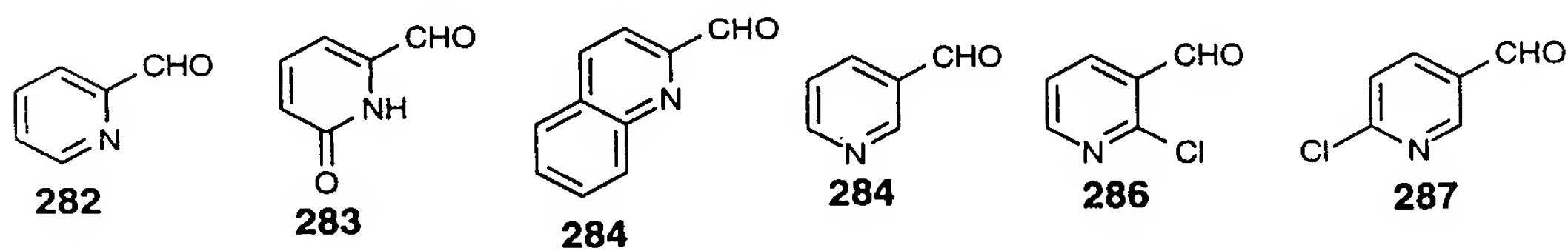
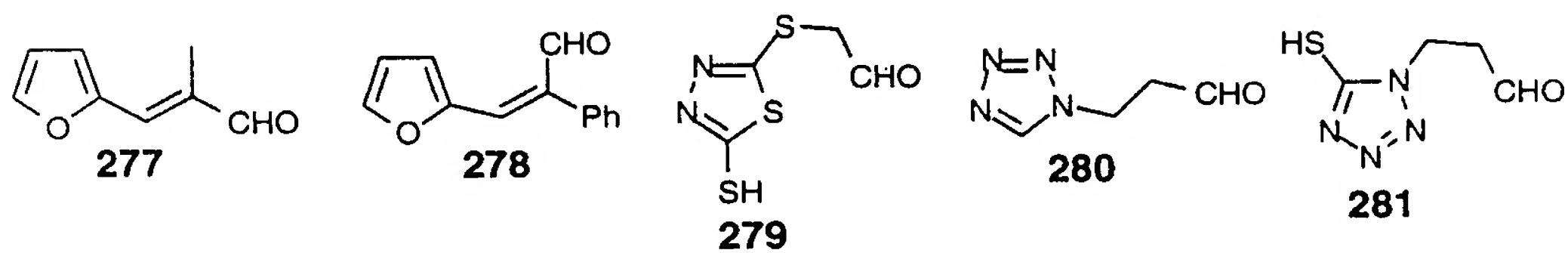
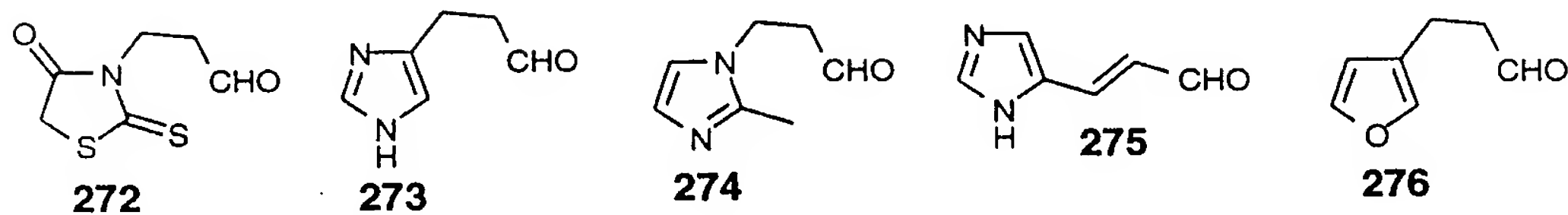




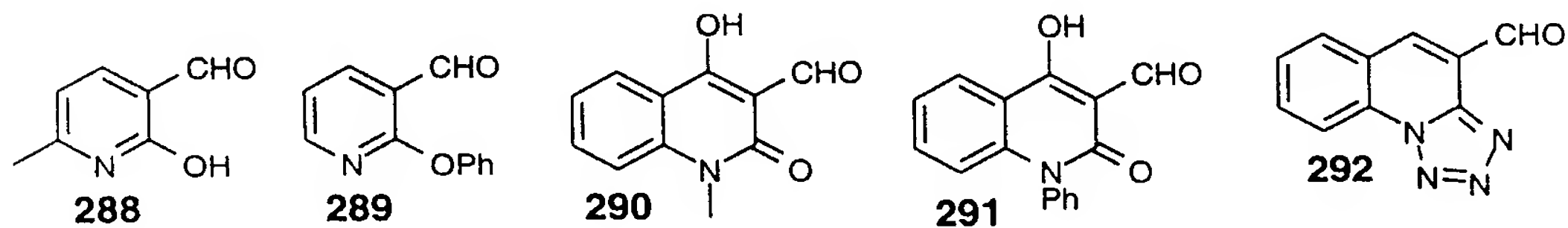
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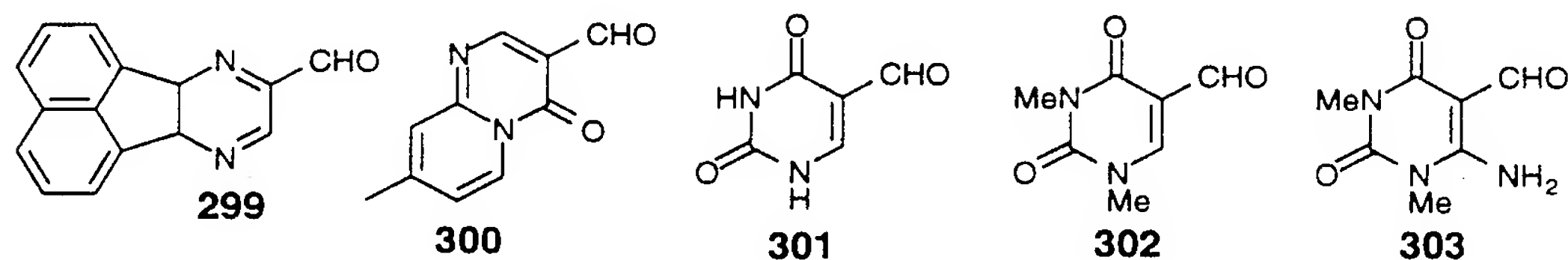
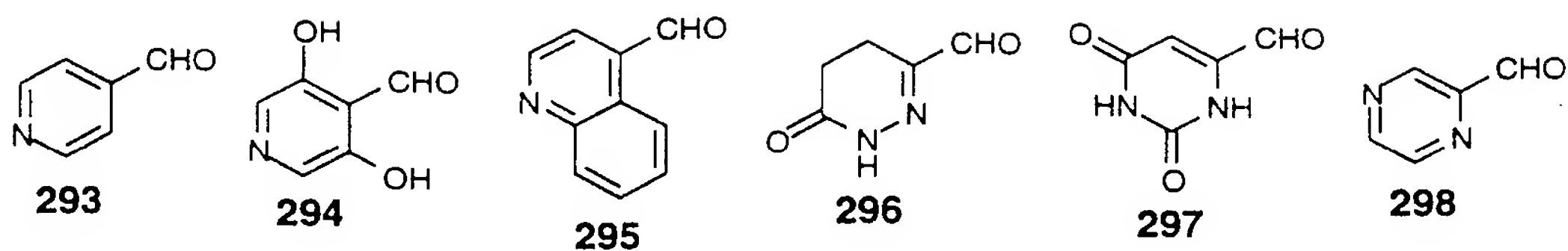


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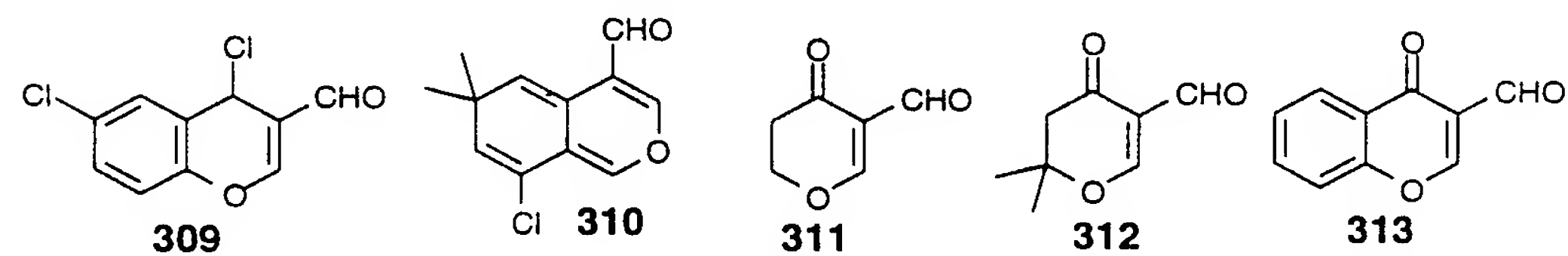
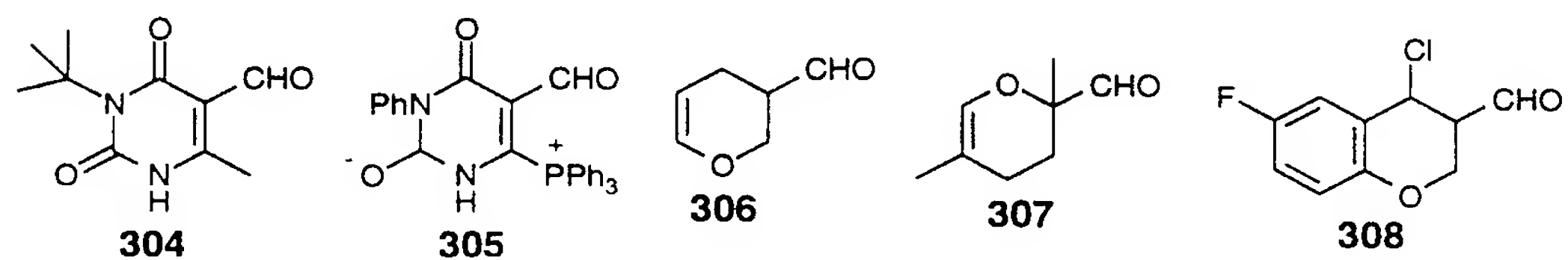


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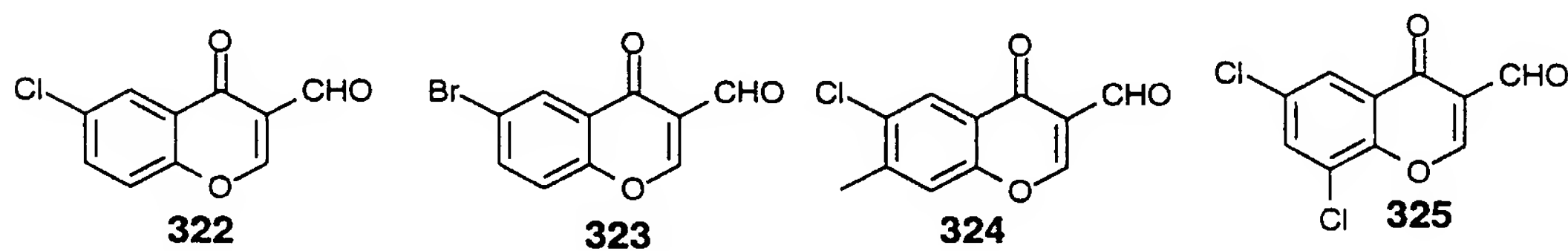
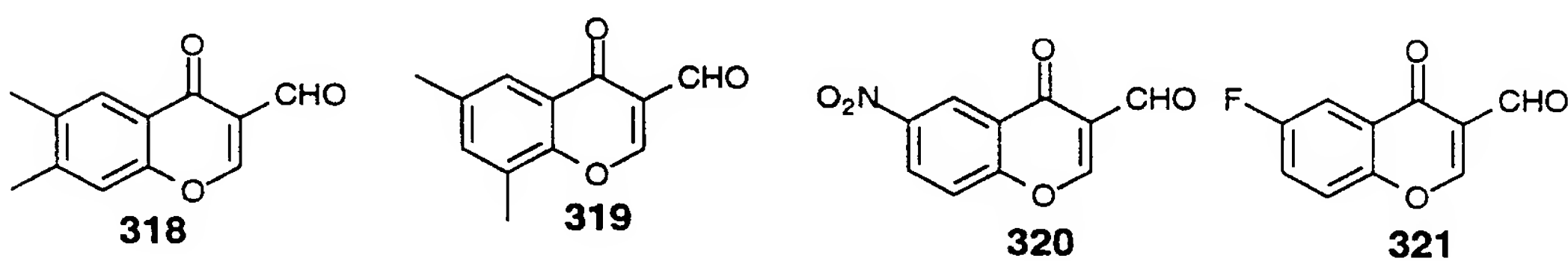
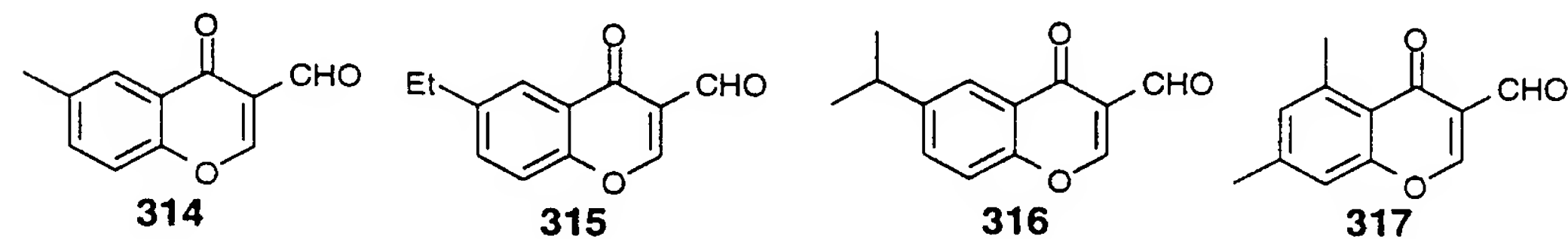




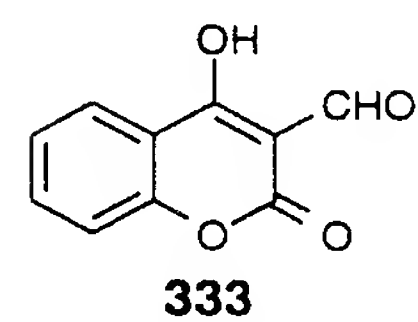
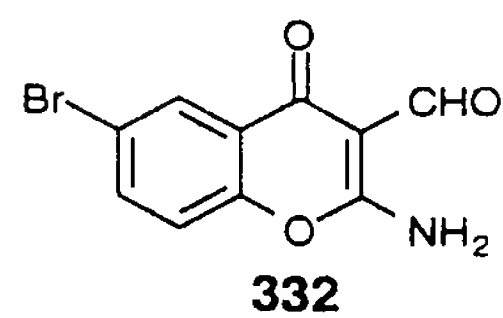
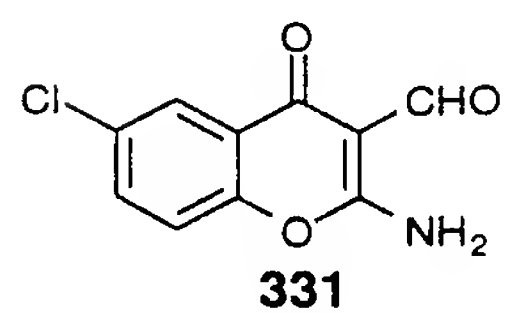
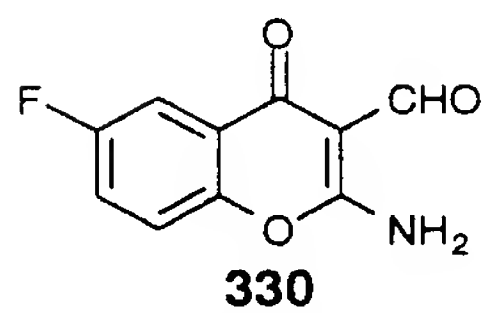
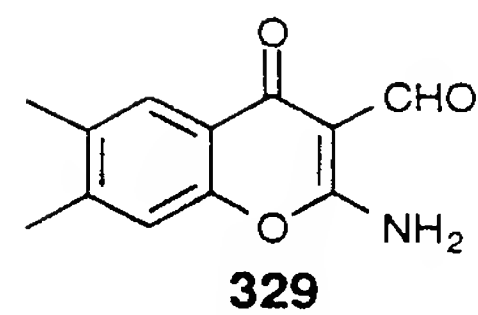
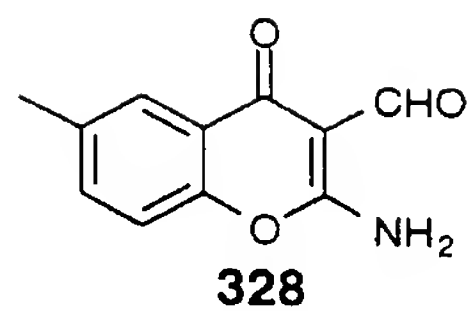
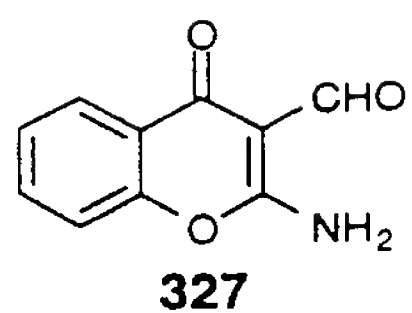
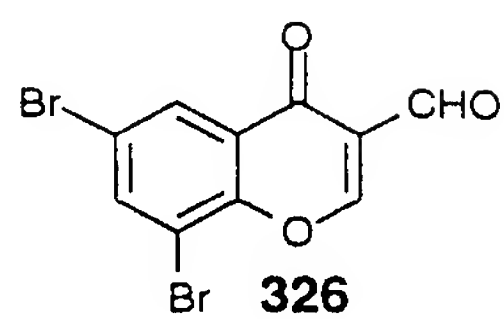
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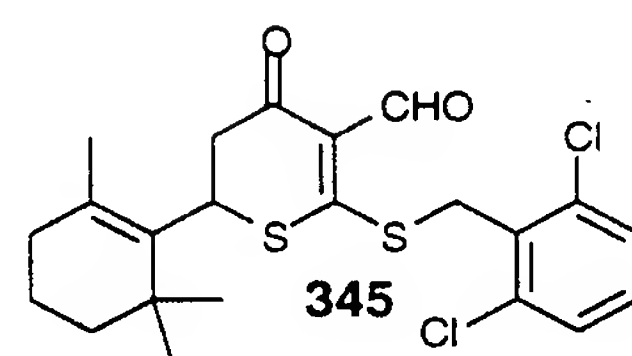
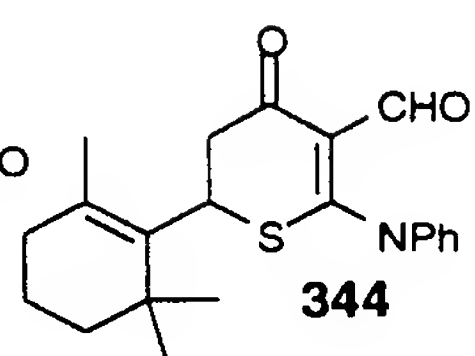
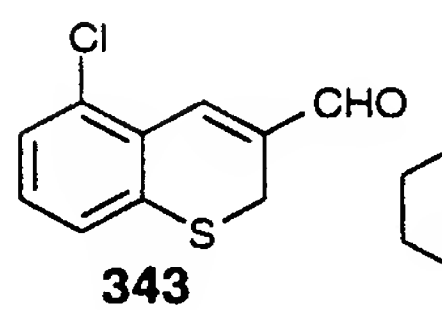
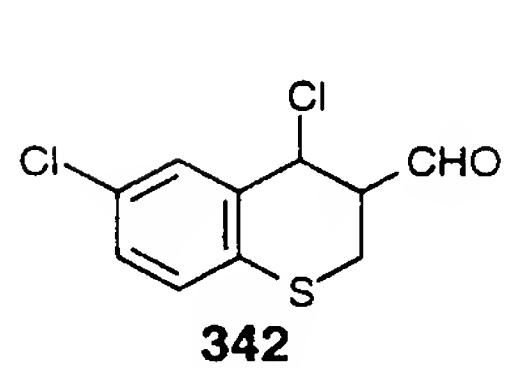
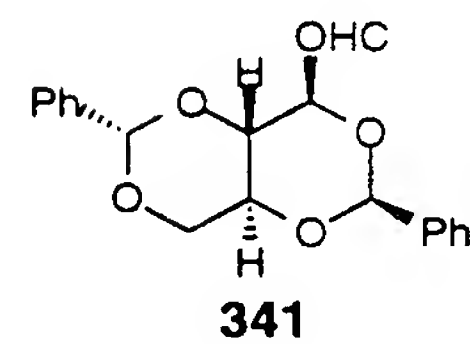
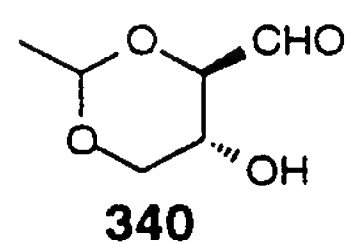
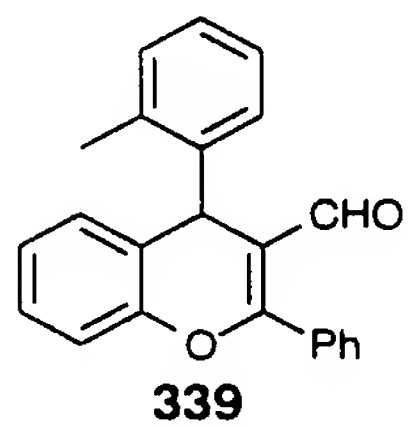
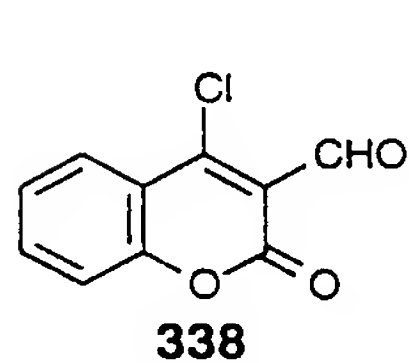
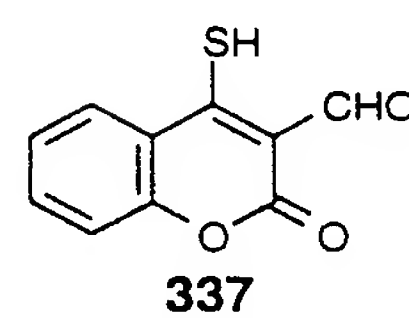
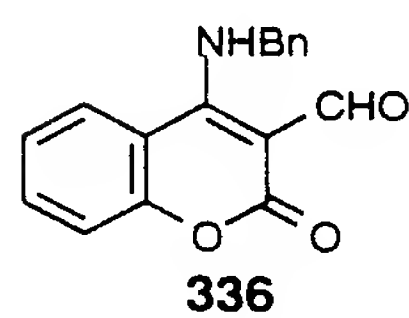
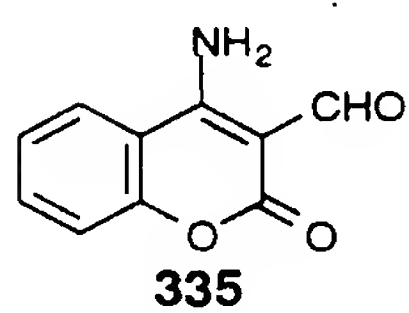
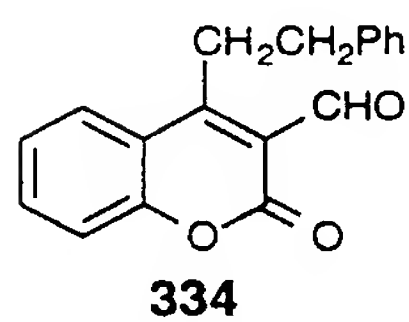
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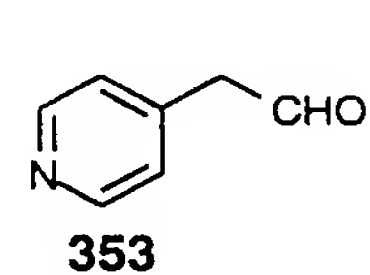
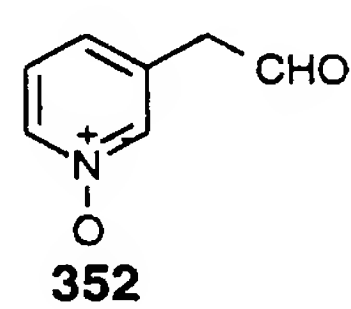
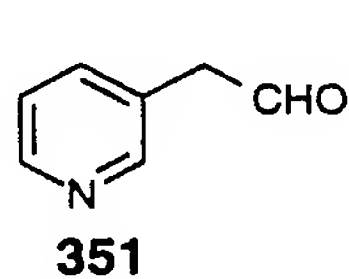
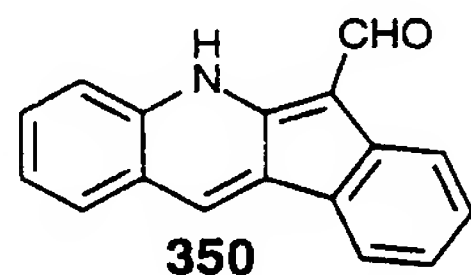
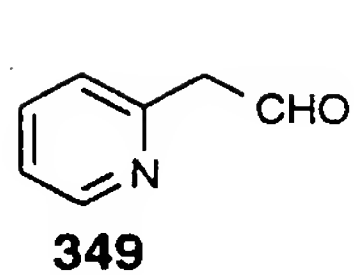
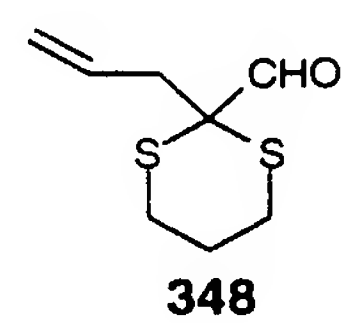
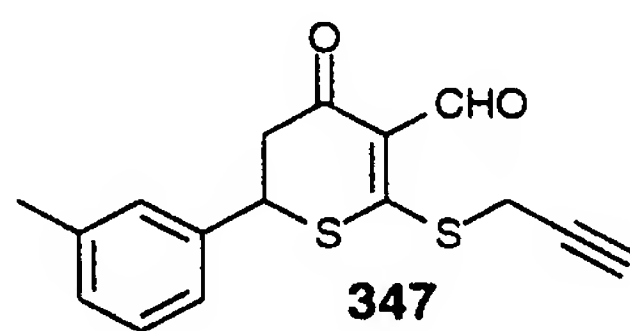
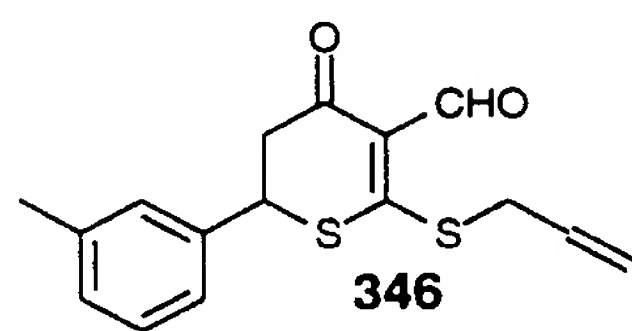
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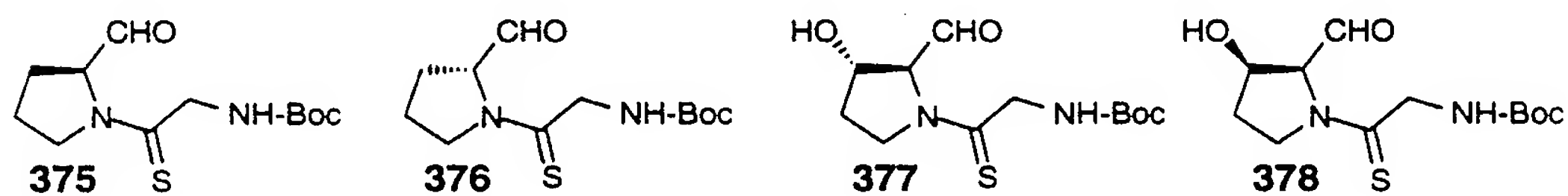
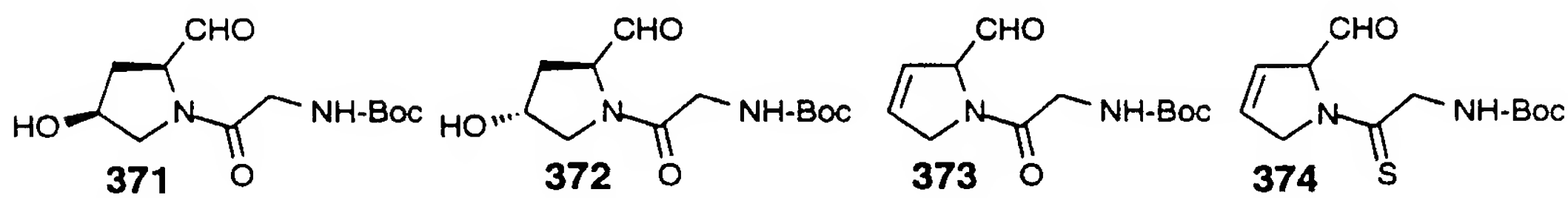
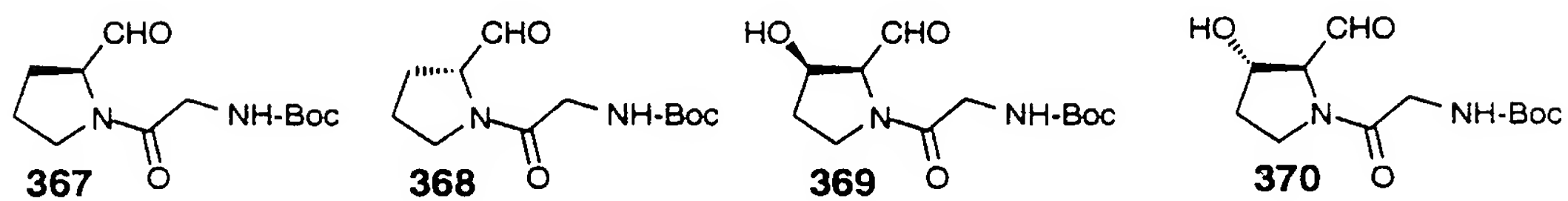
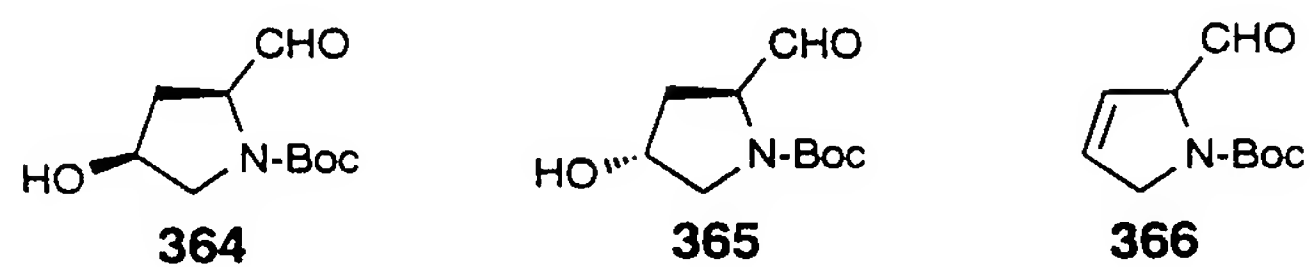
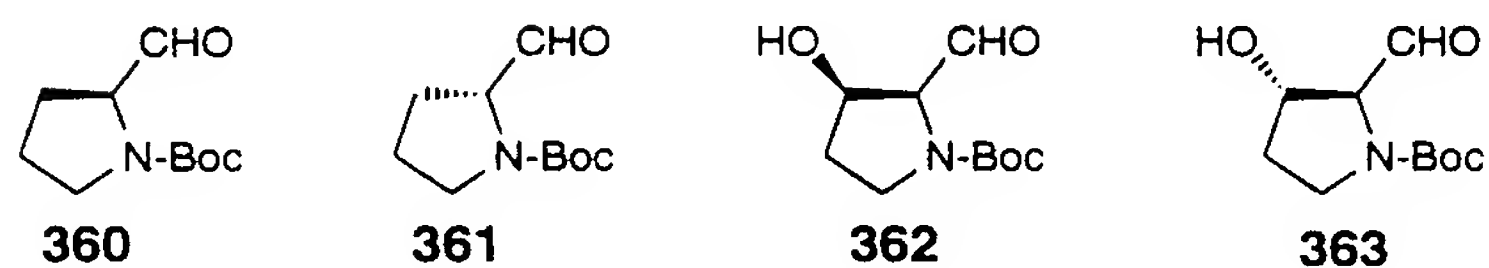
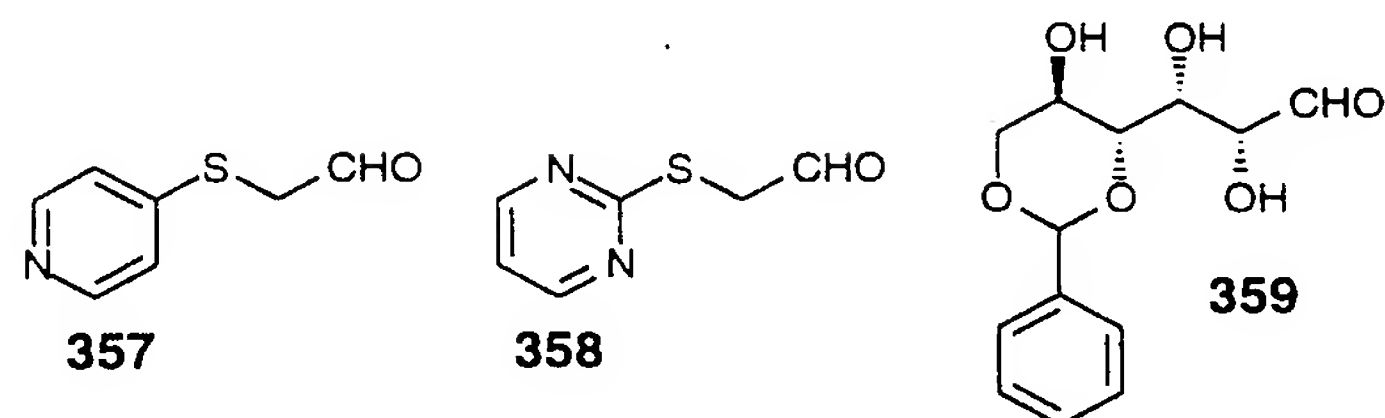
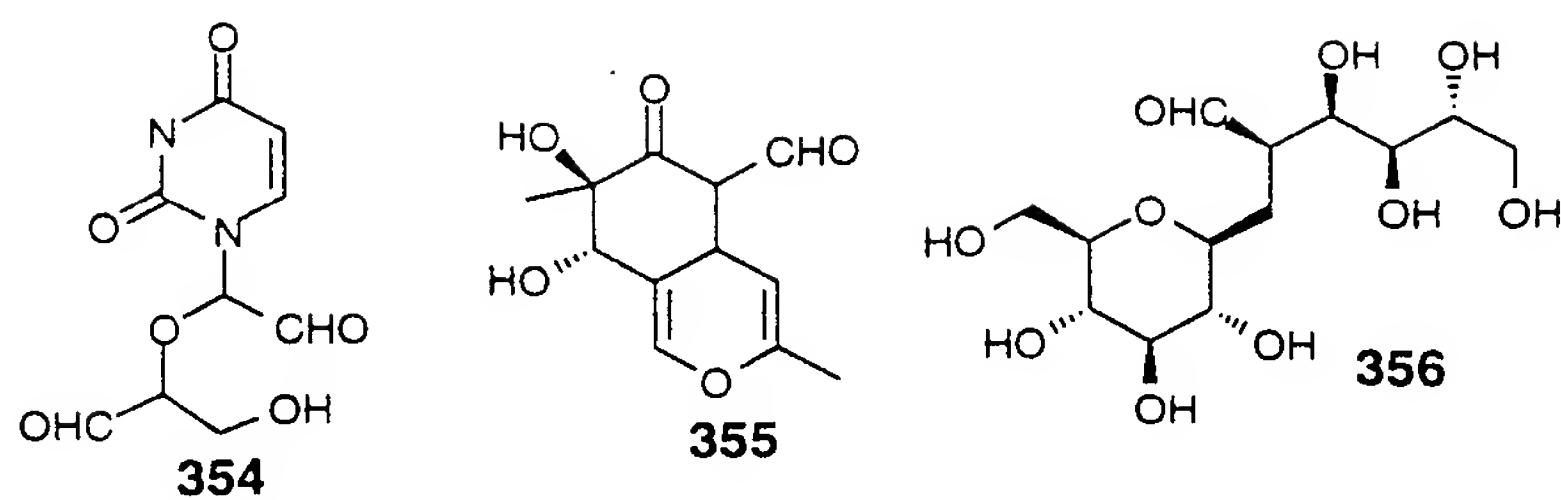
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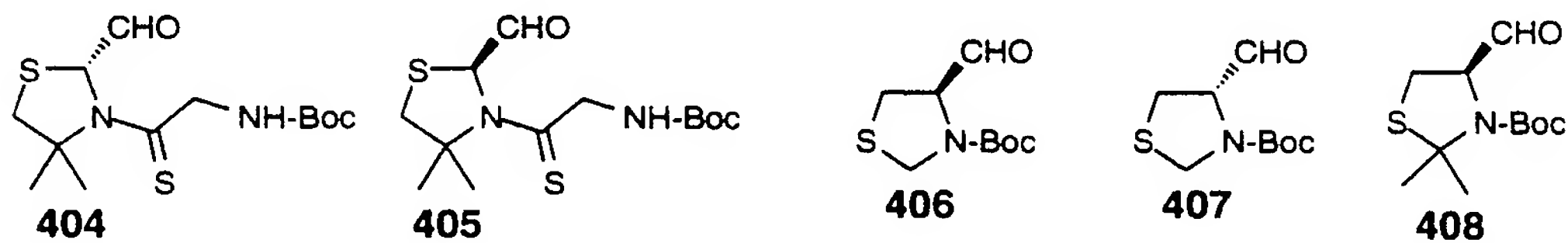
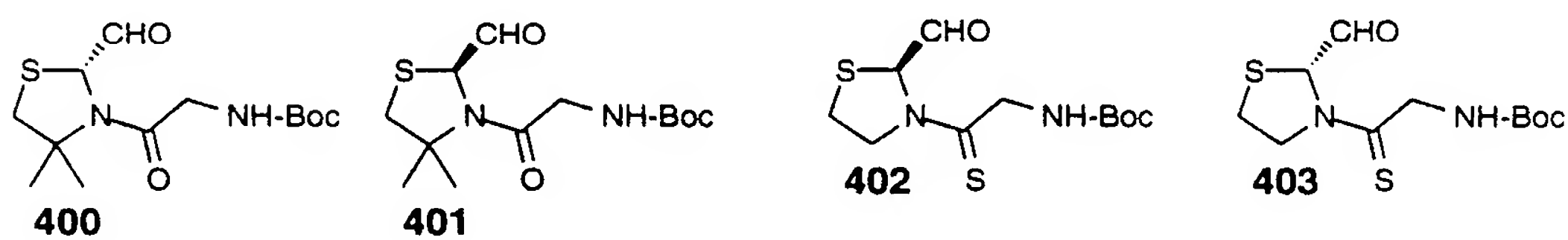
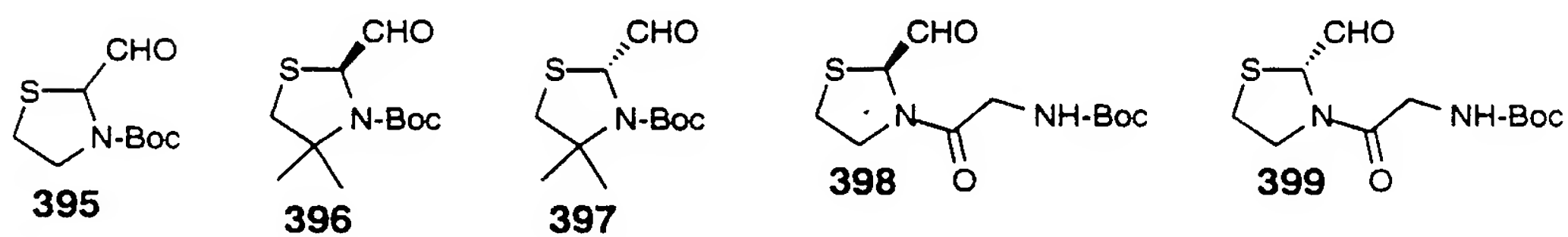
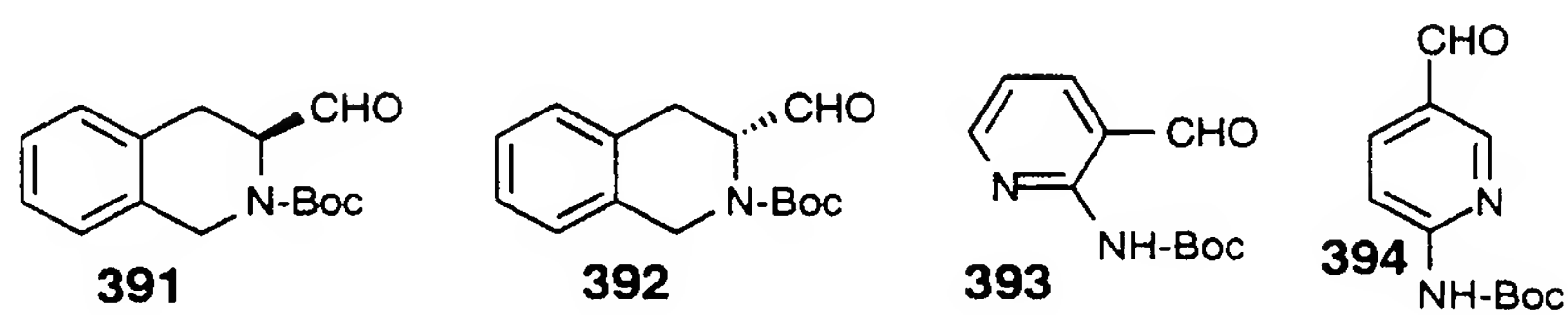
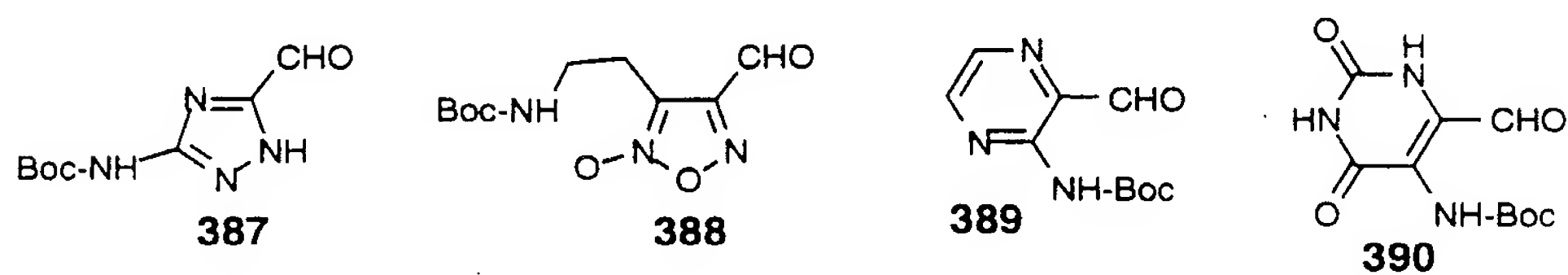
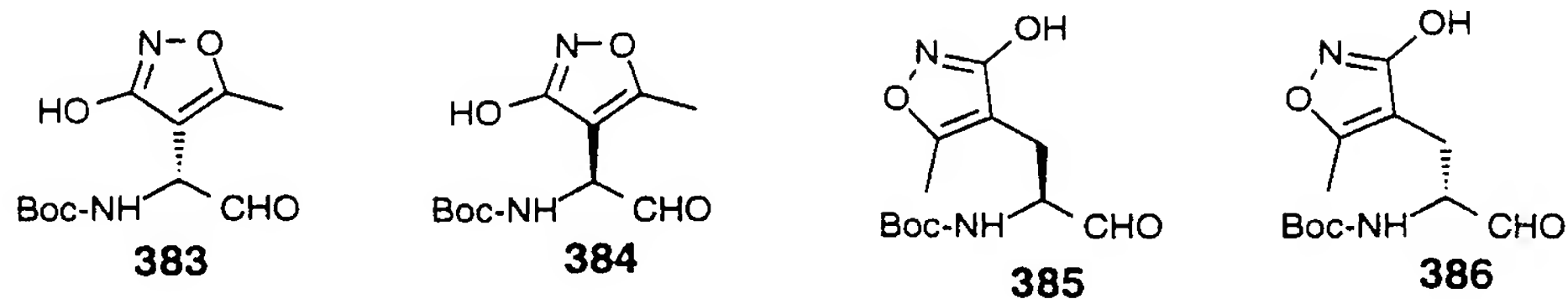
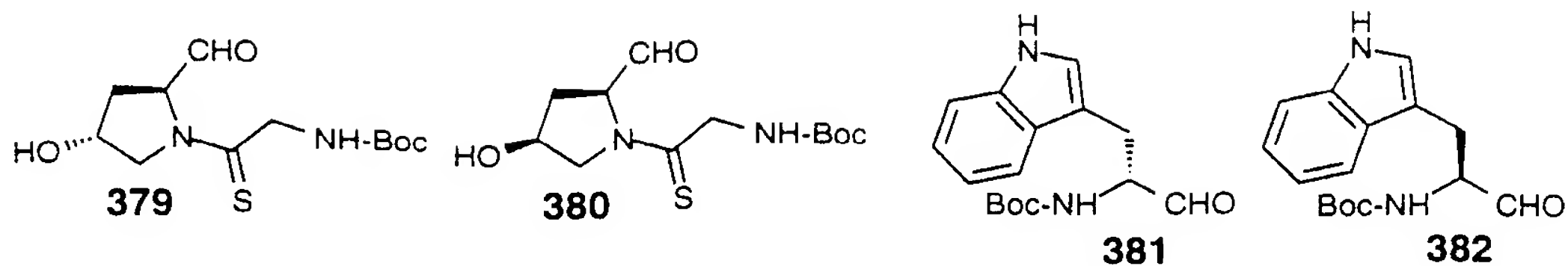


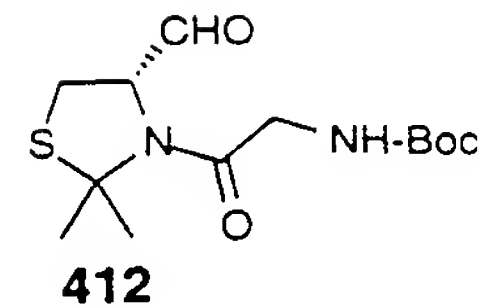
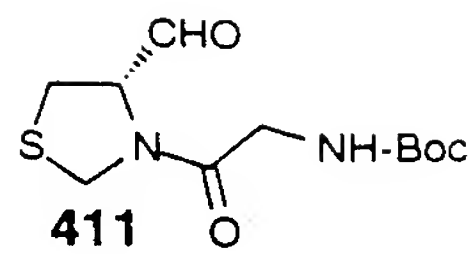
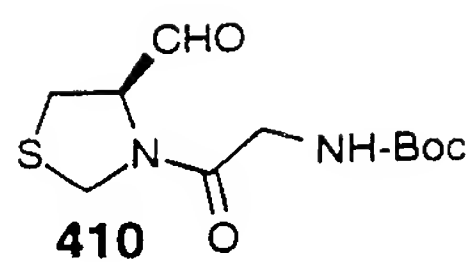
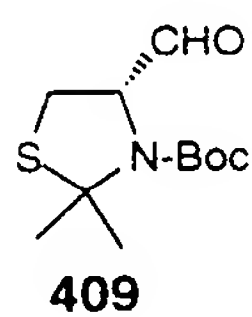
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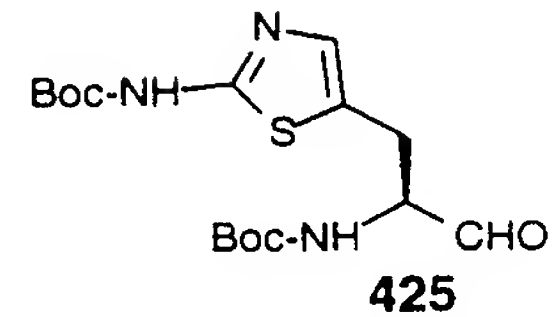
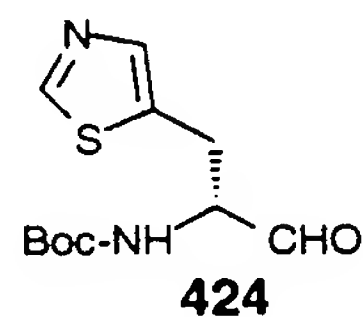
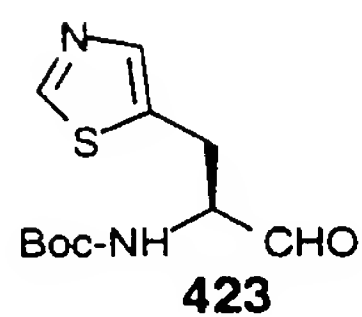
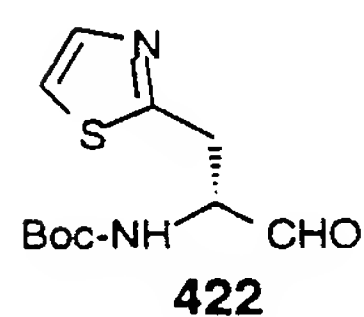
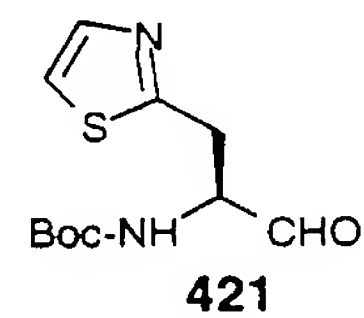
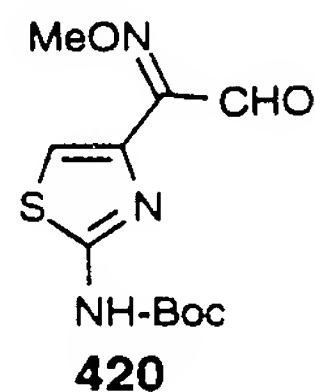
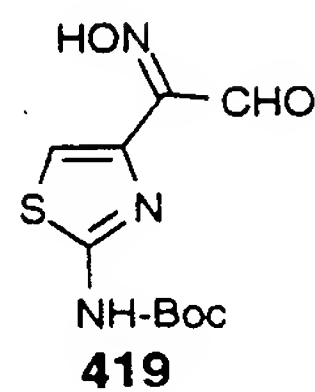
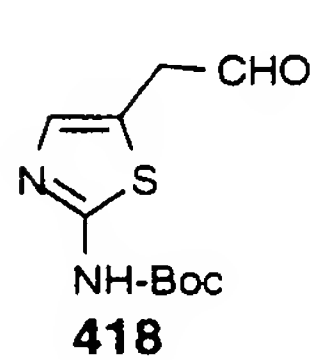
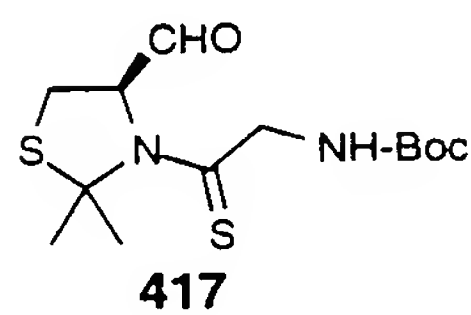
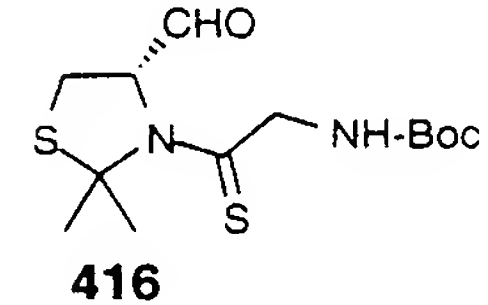
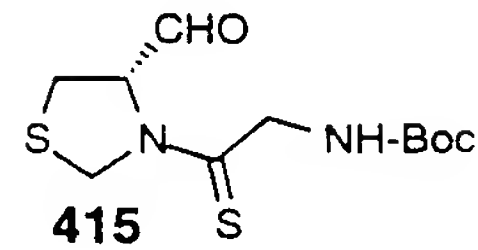
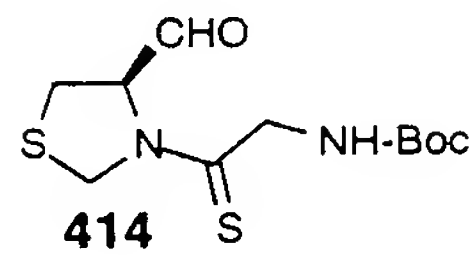
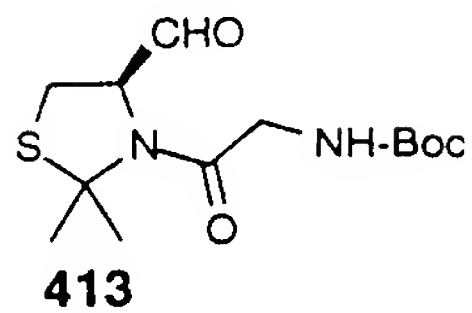
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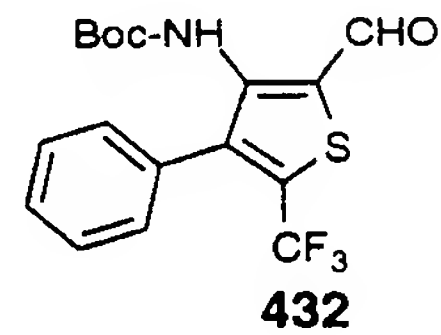
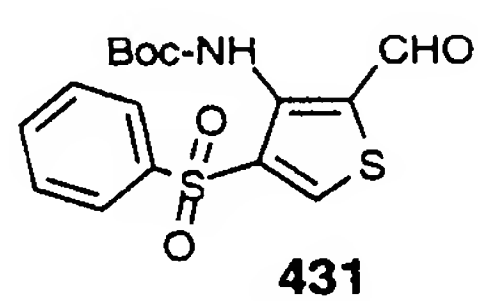
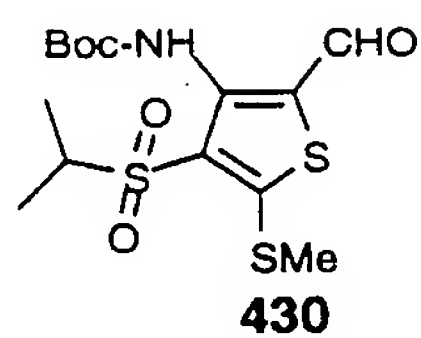
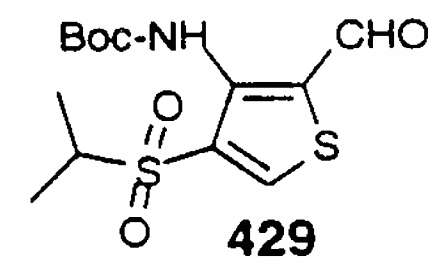
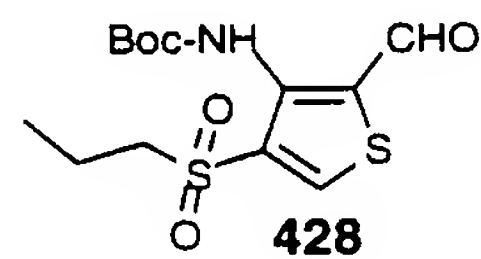
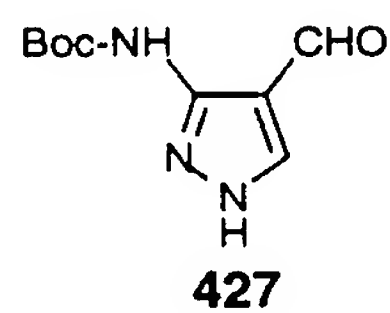
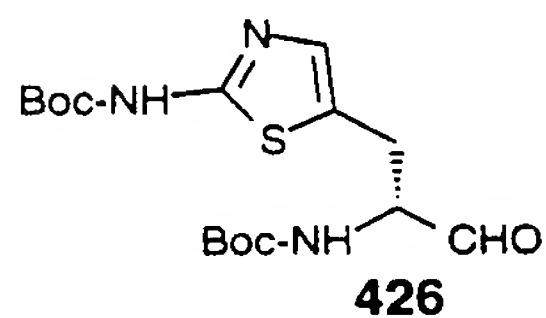




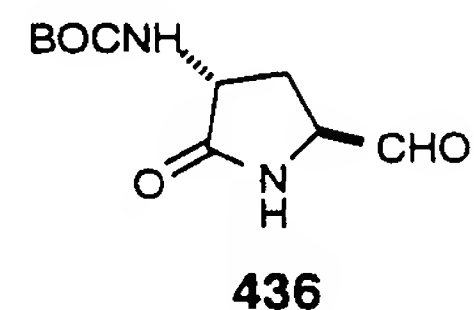
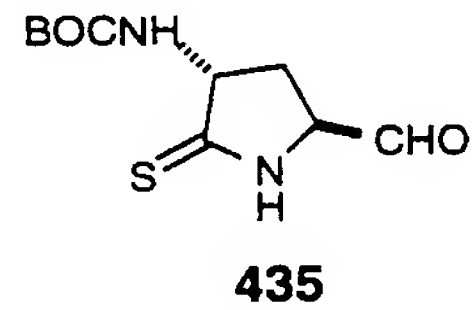
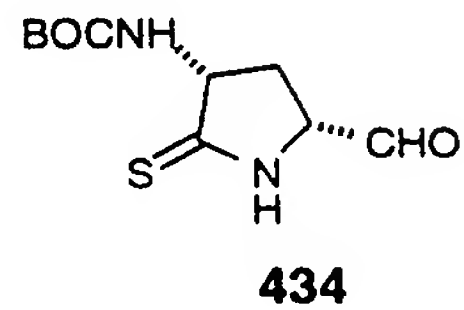
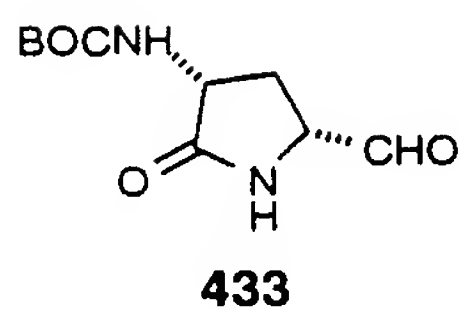
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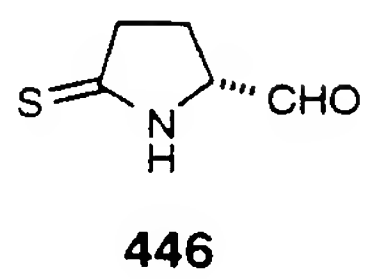
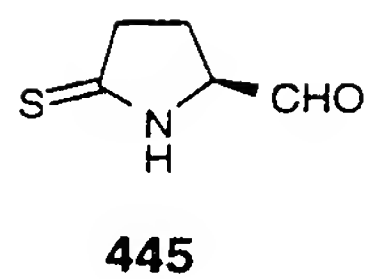
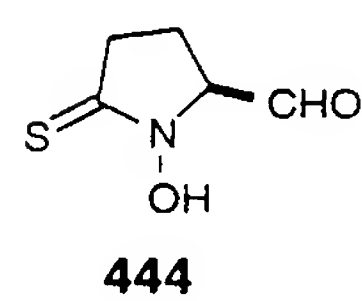
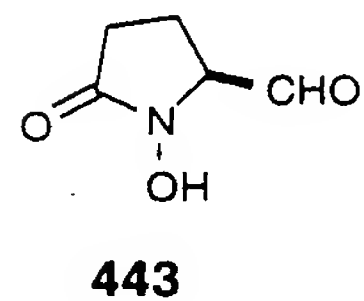
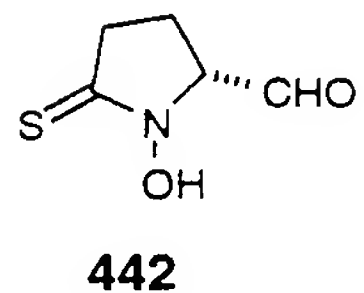
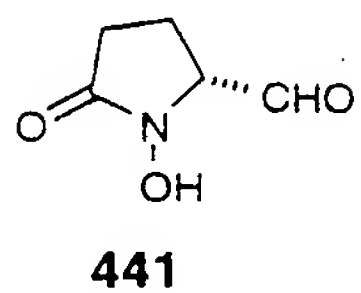
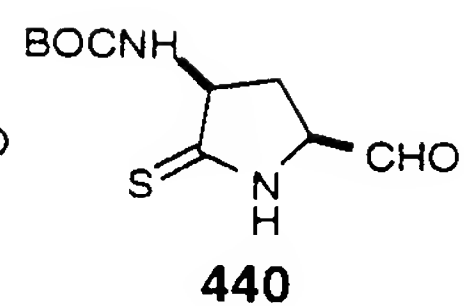
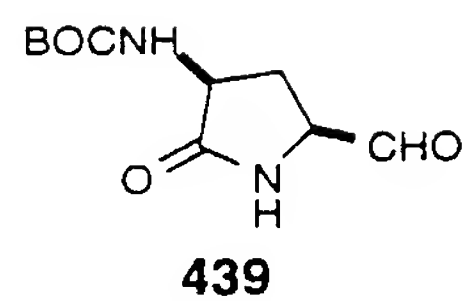
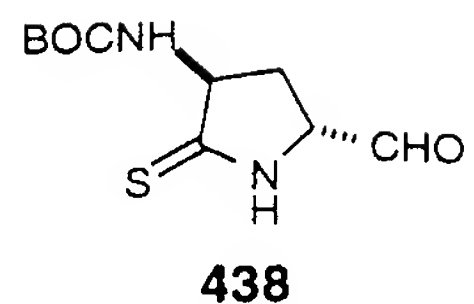
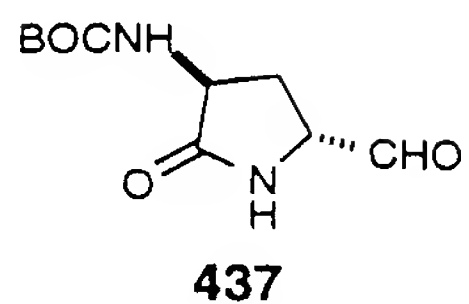
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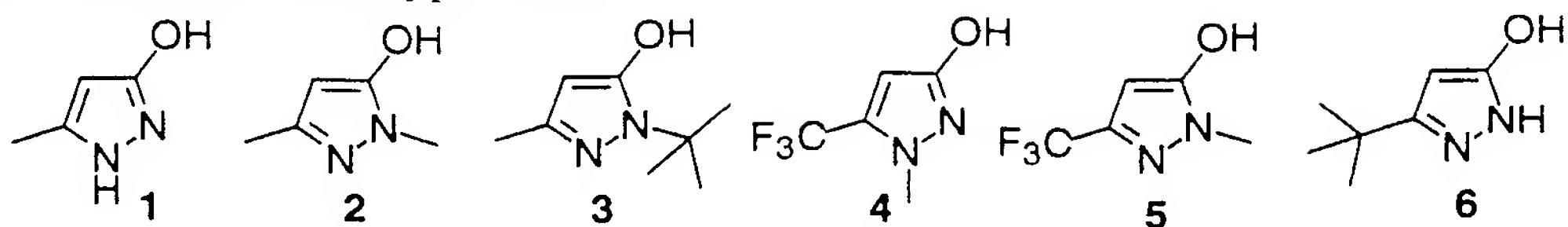




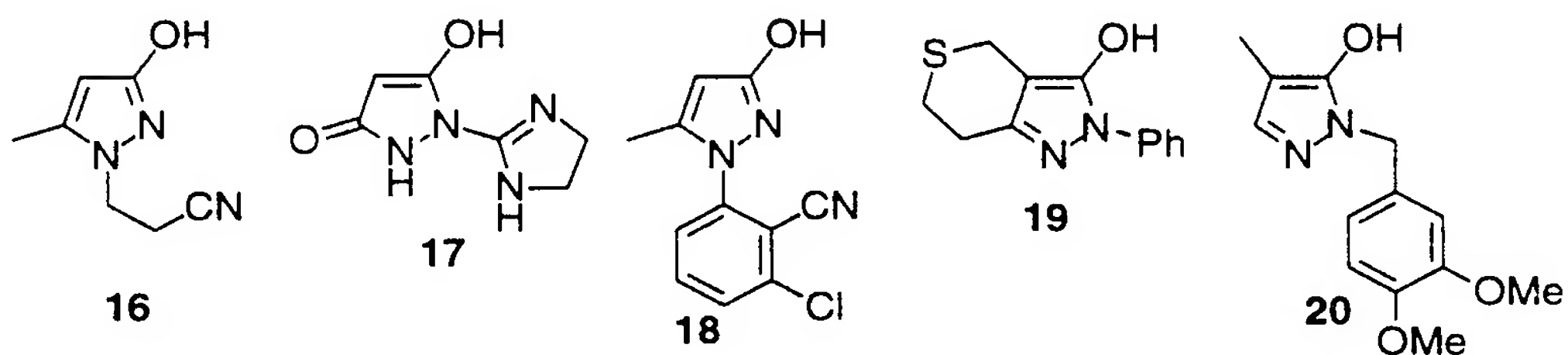
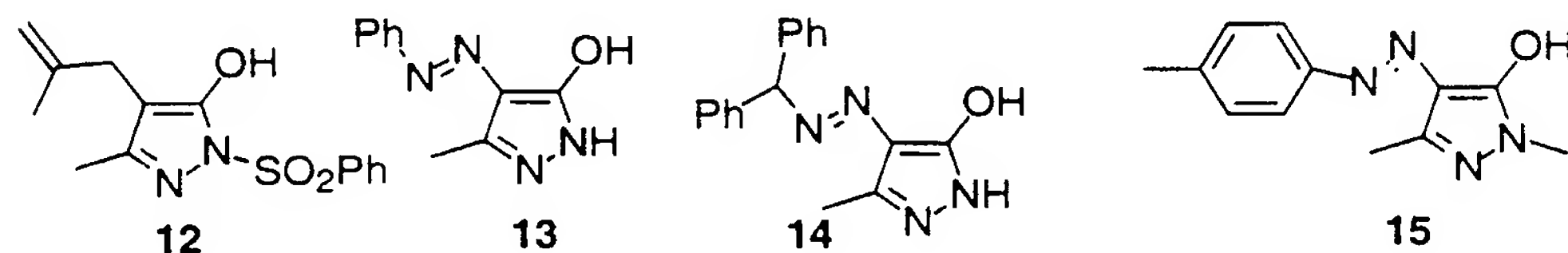
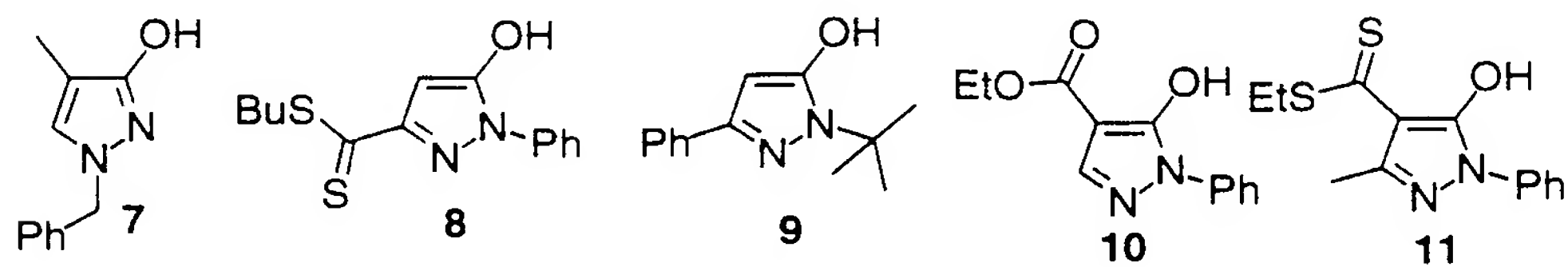


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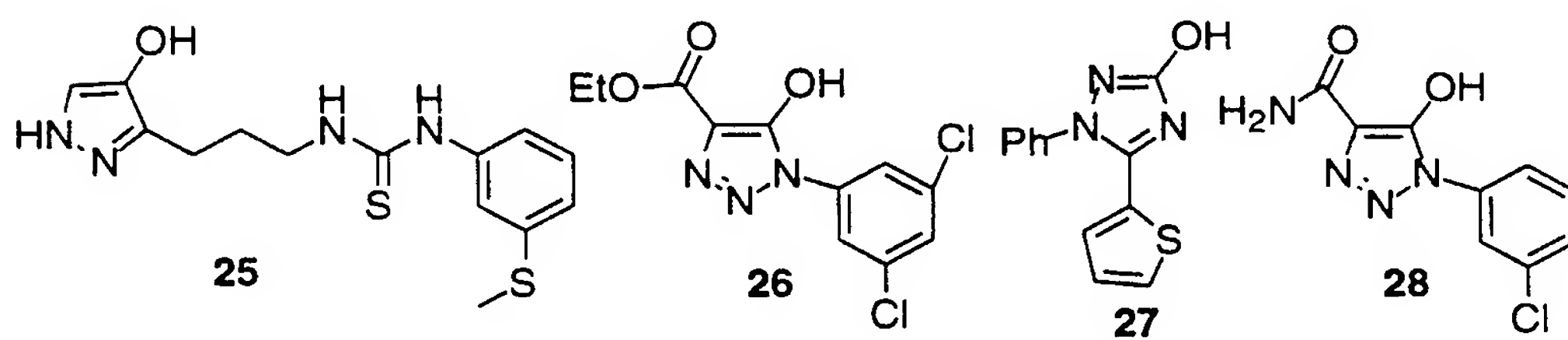
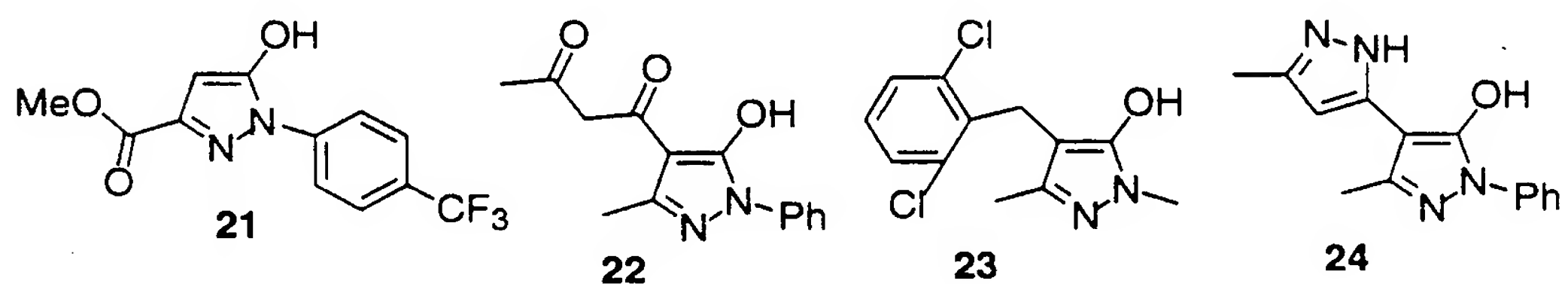
Table 15. Alcohols of the type A-OH



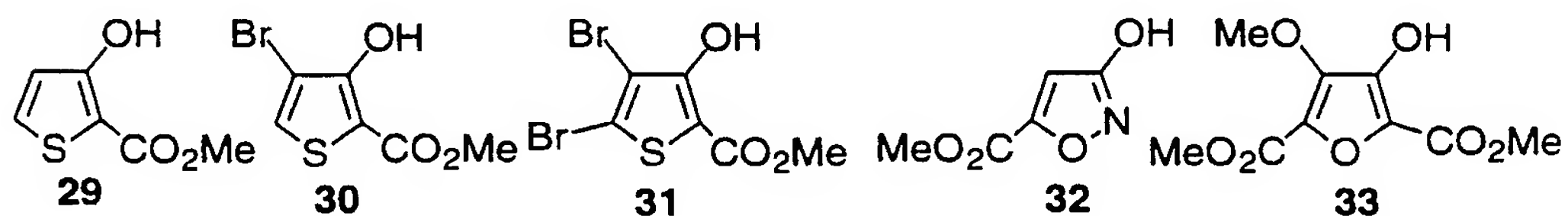
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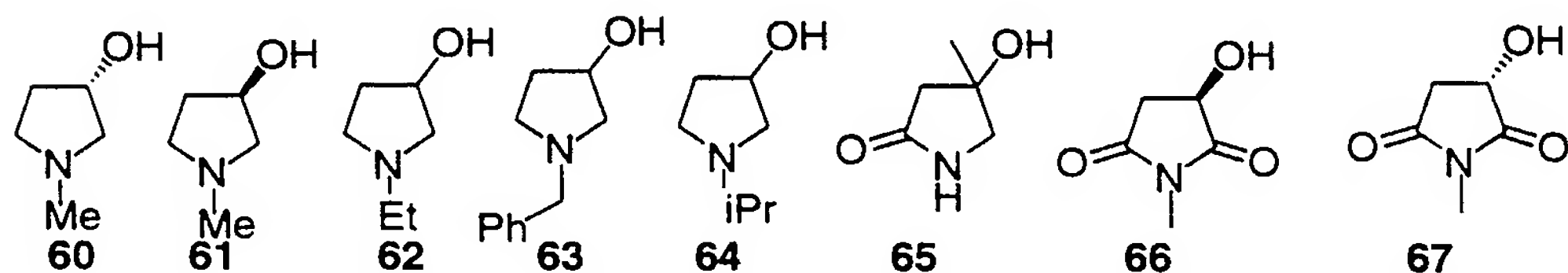
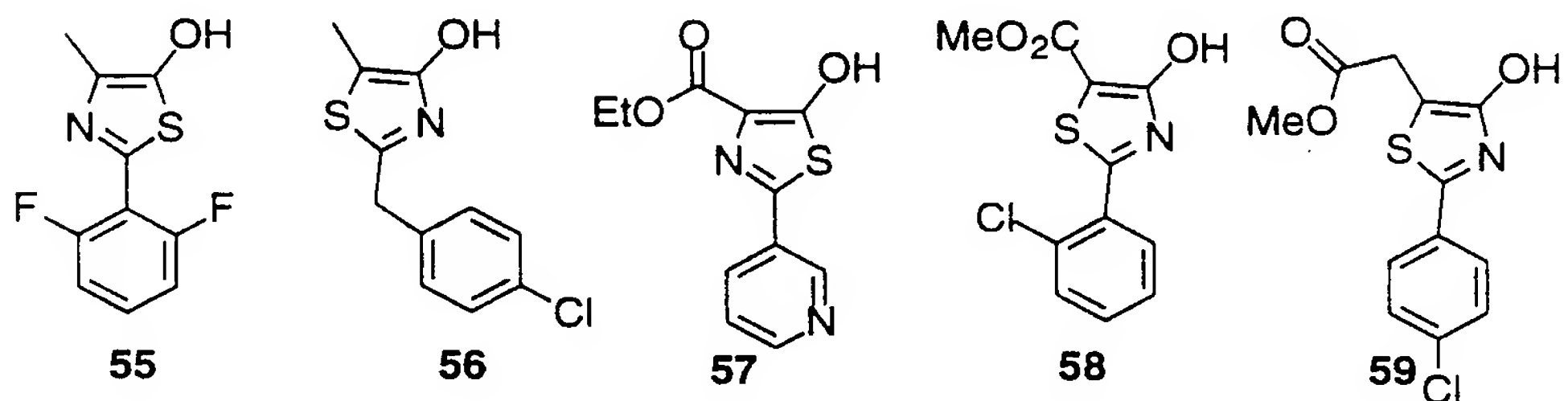
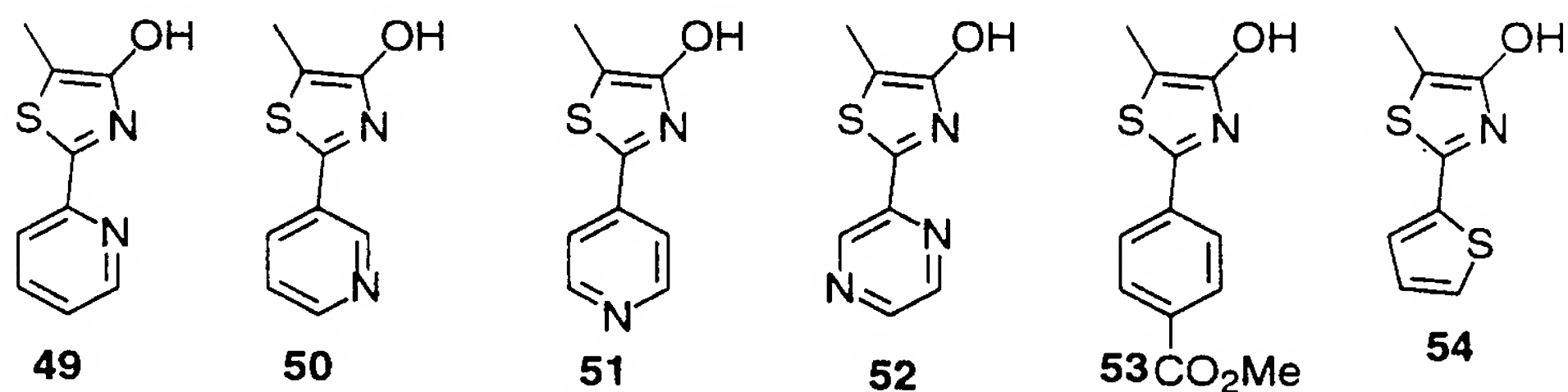
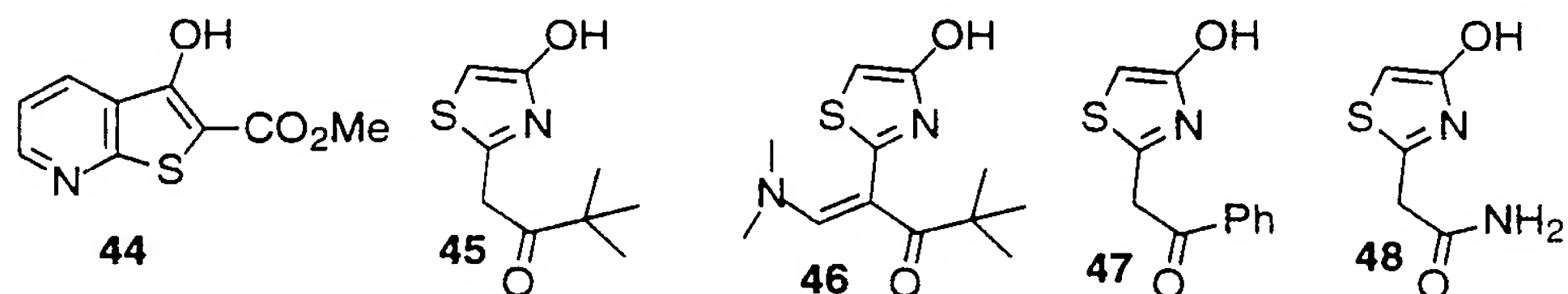
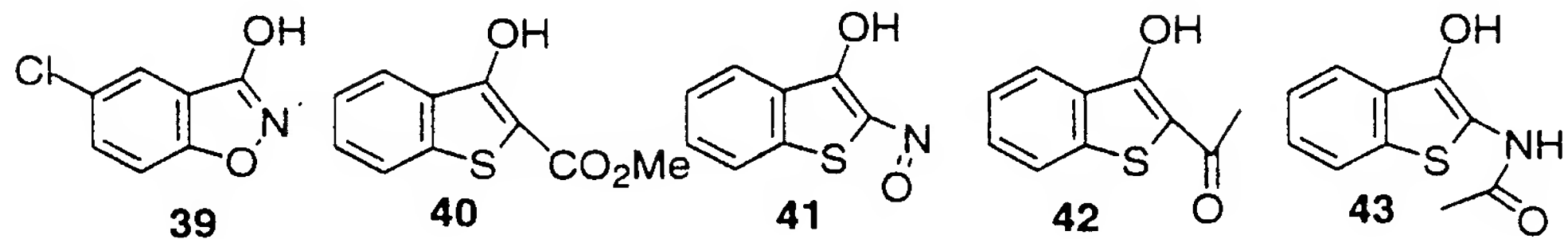
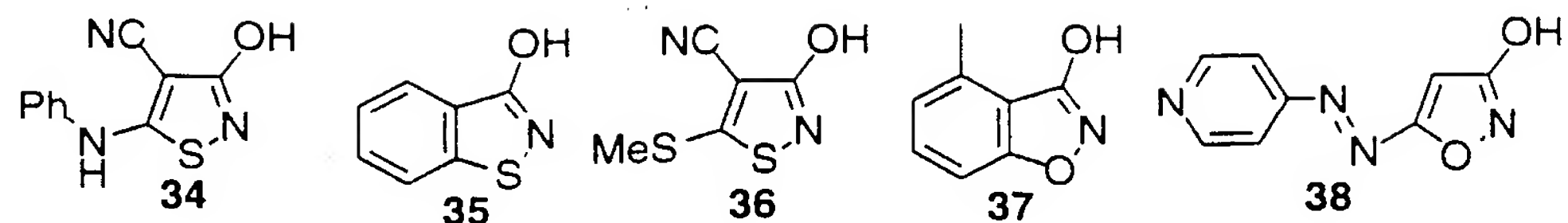


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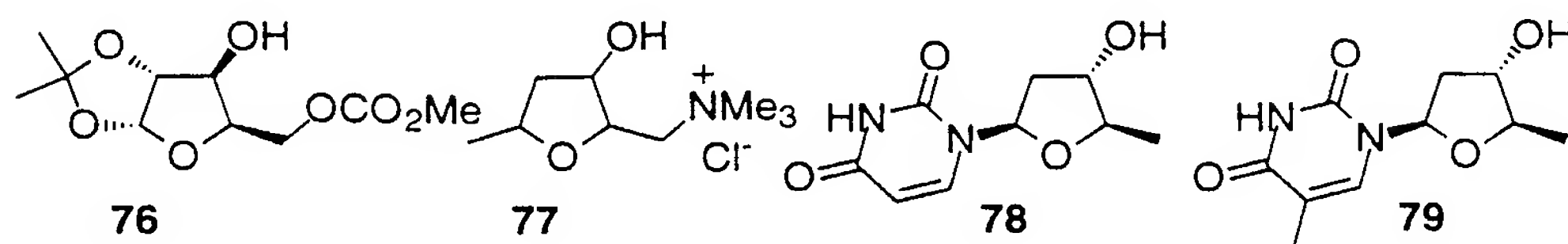
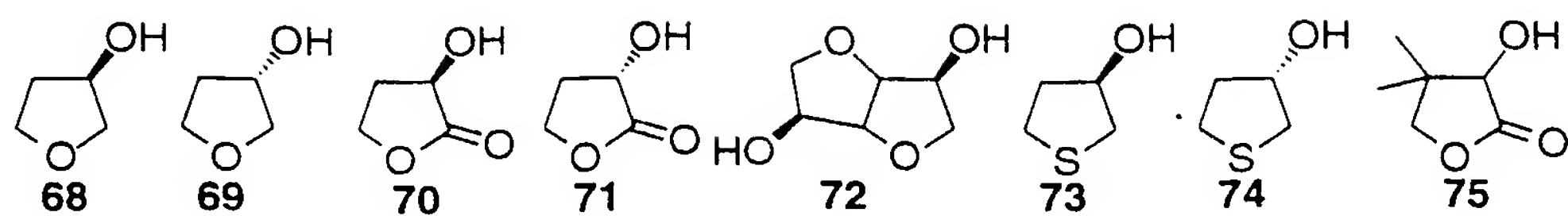


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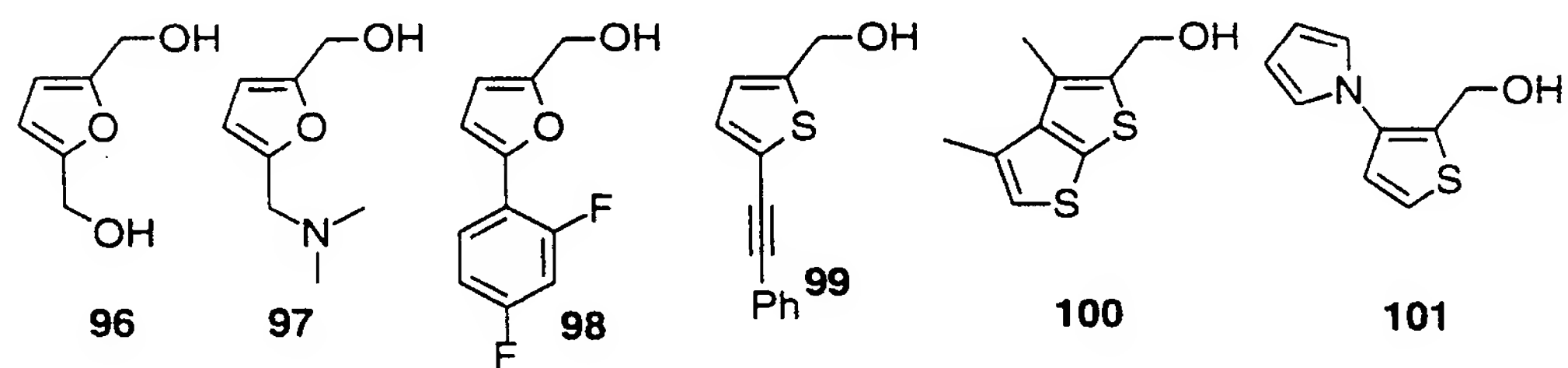
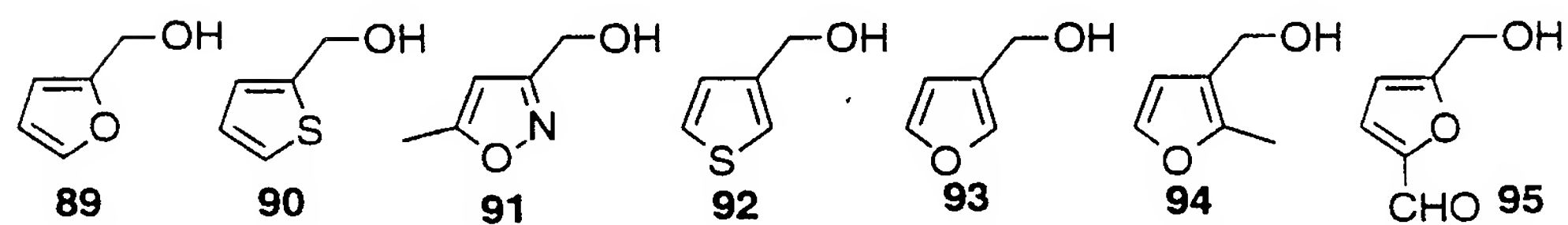
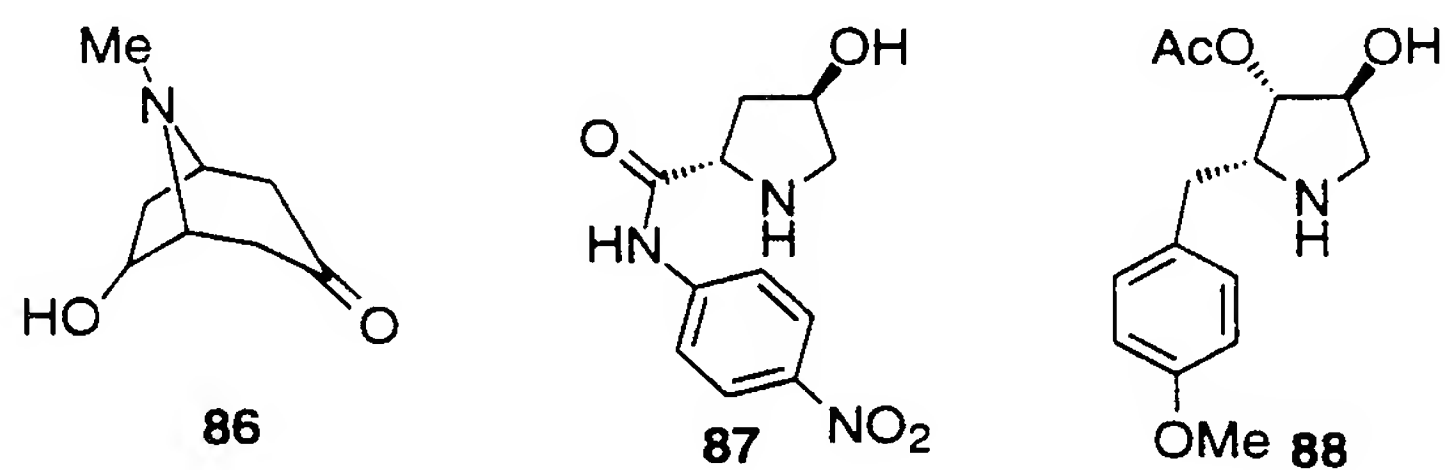
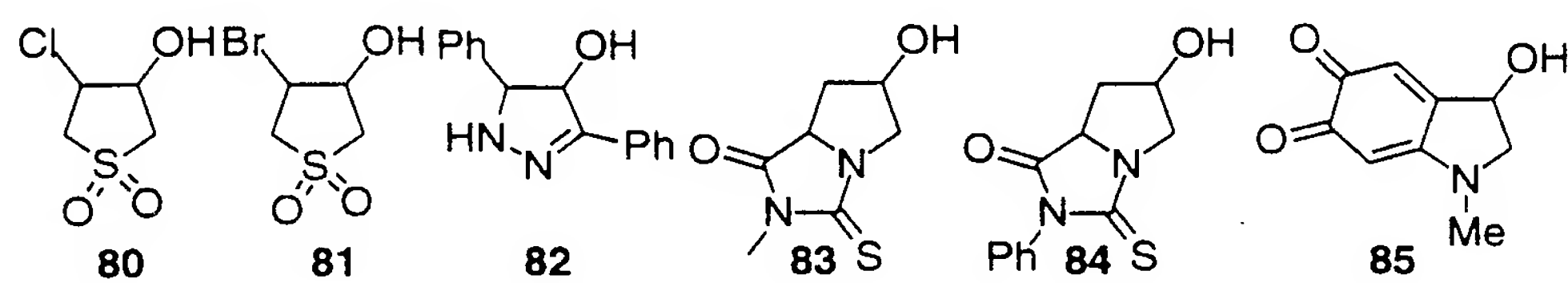




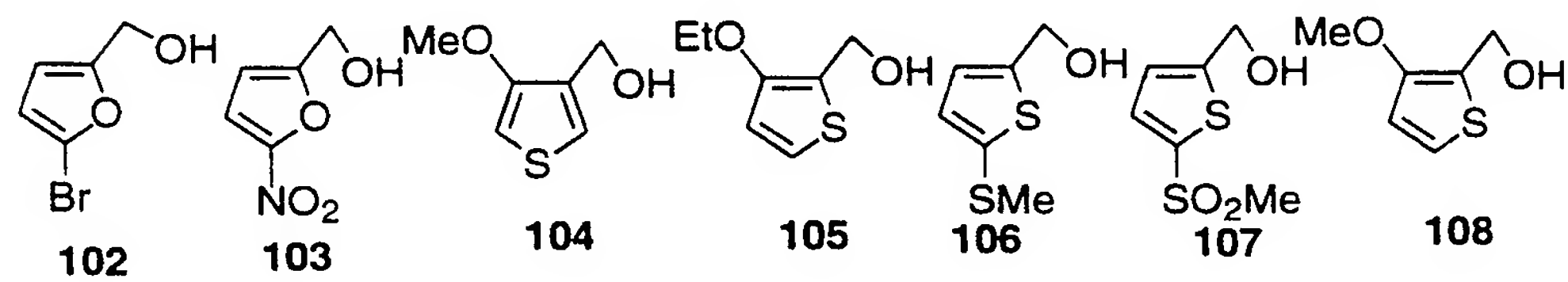
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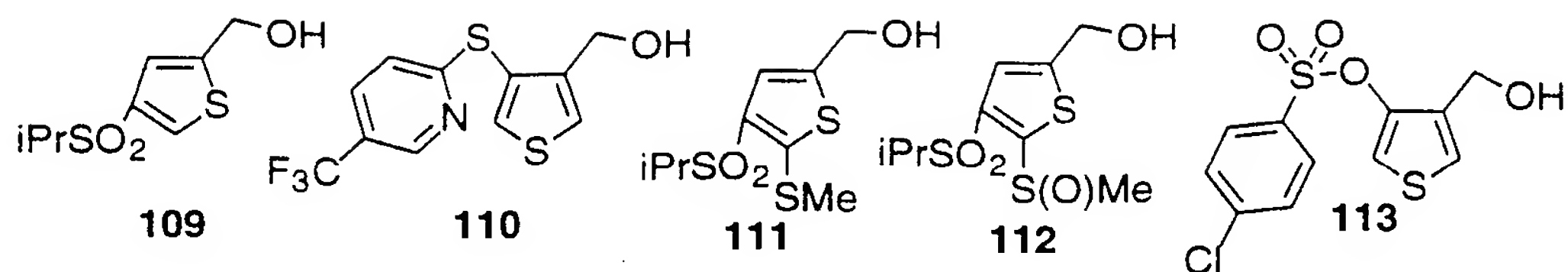


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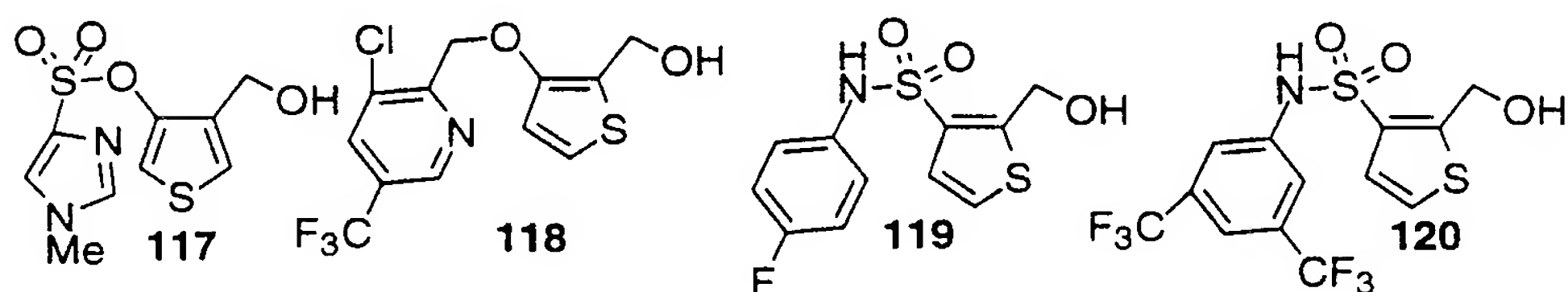
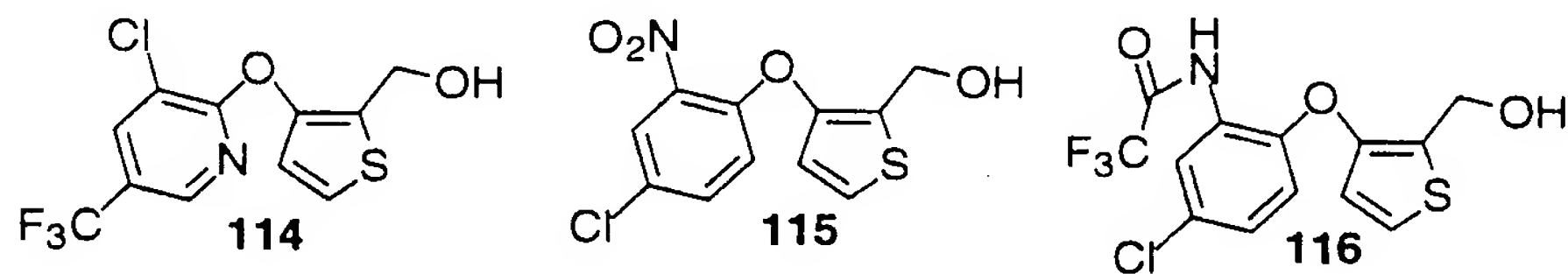


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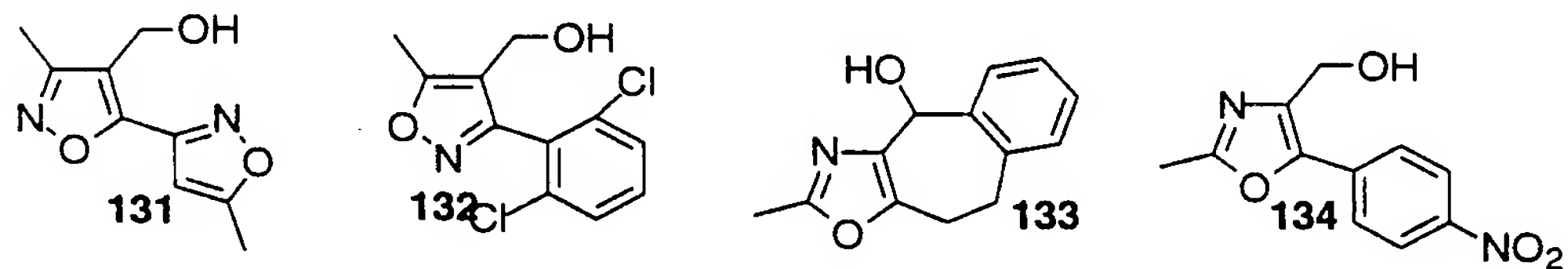
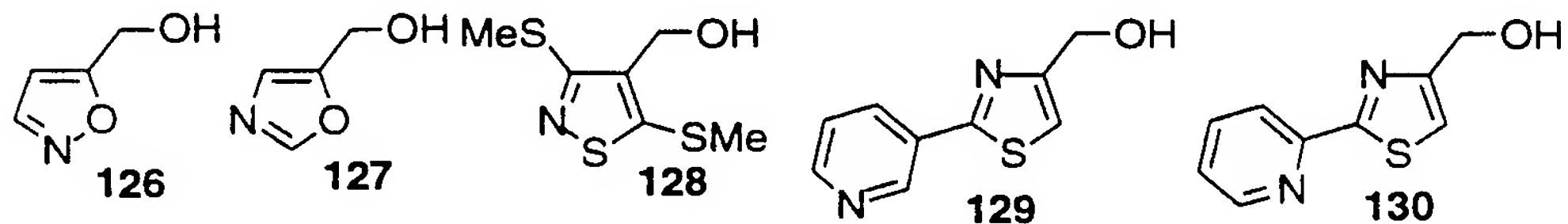
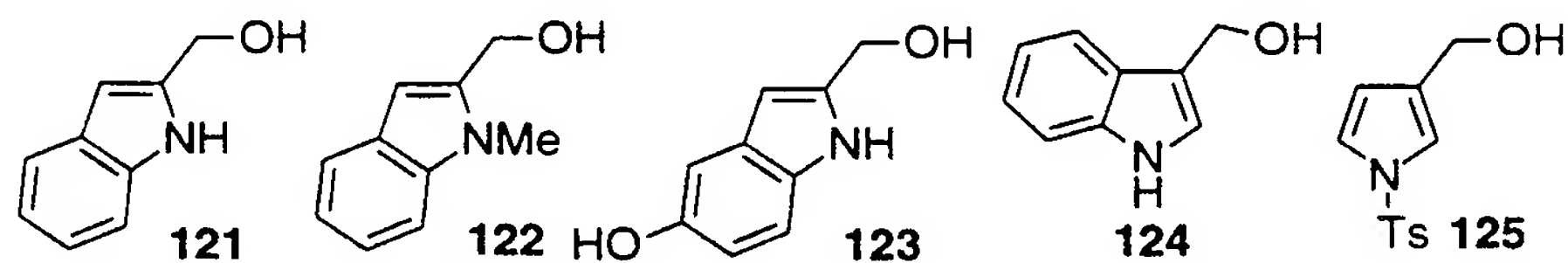




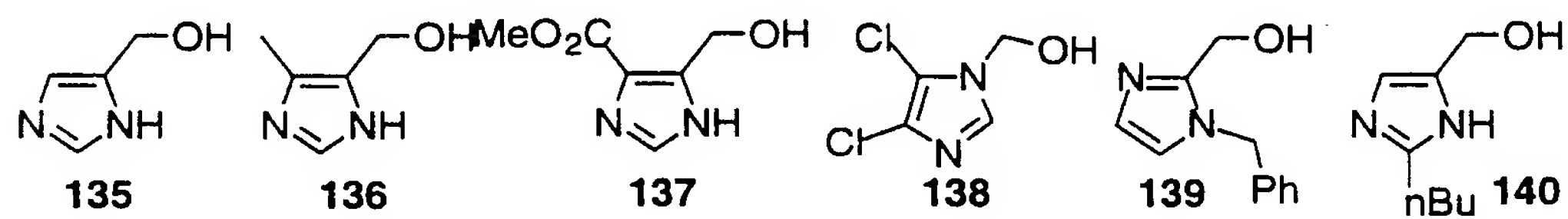
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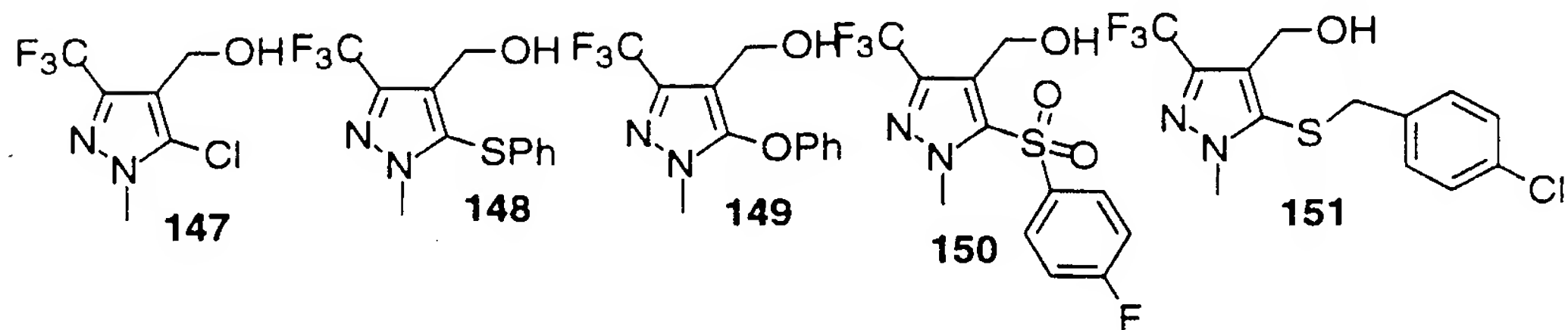
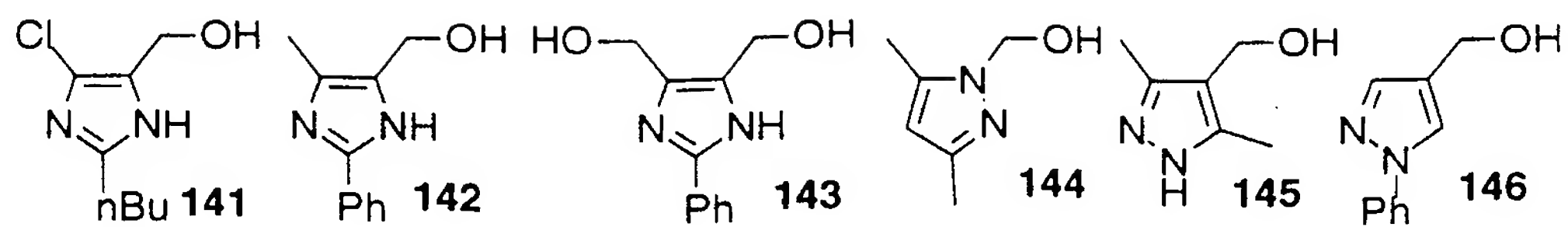


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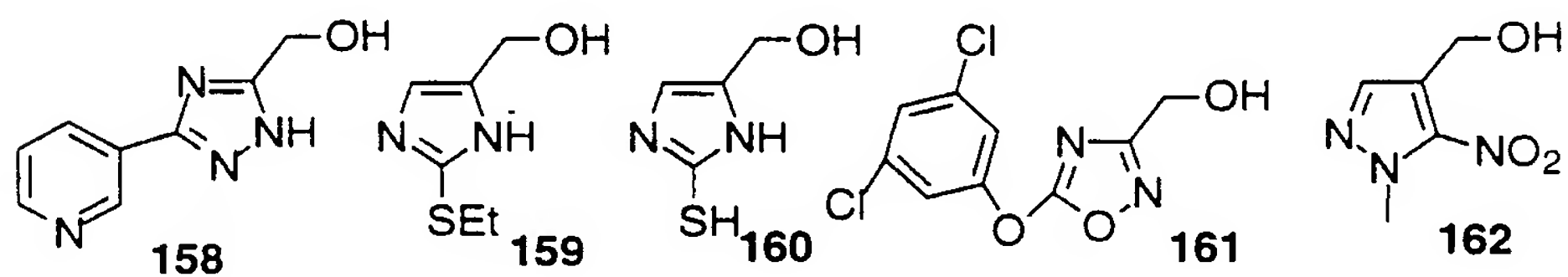
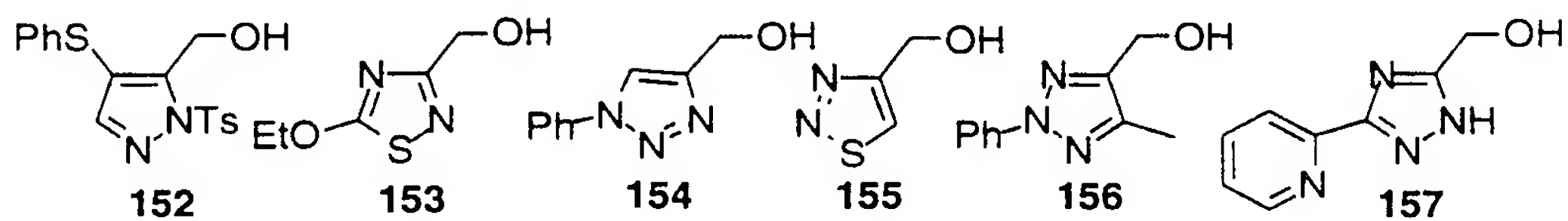


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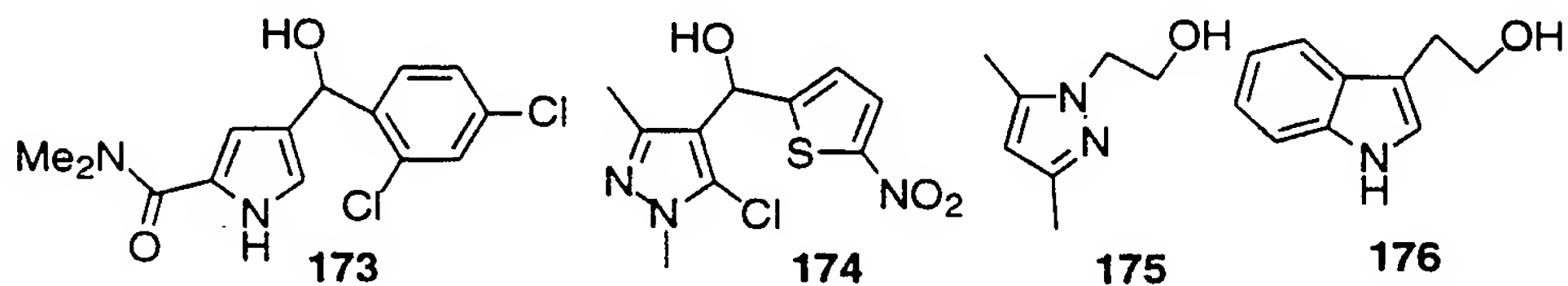
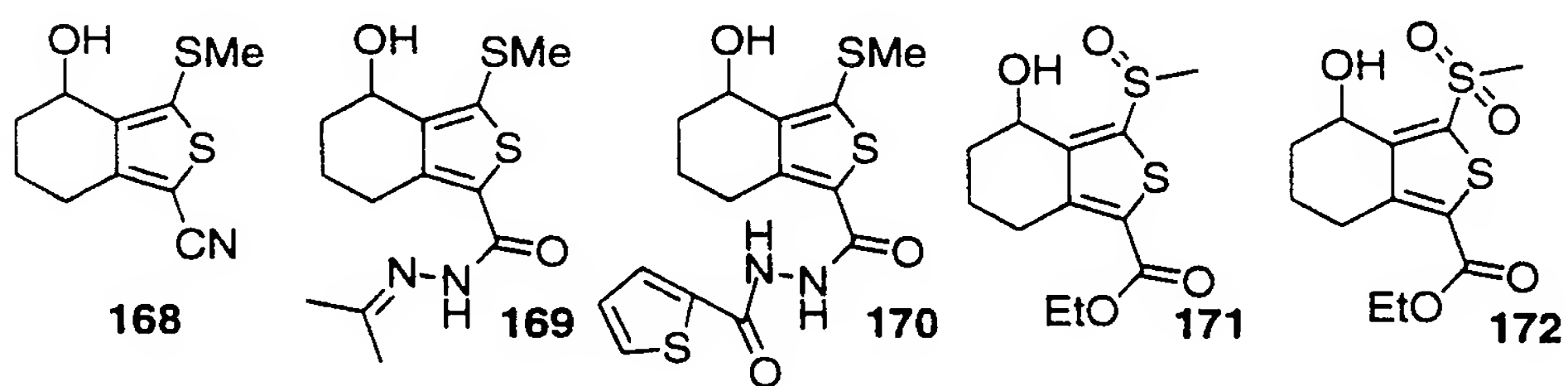
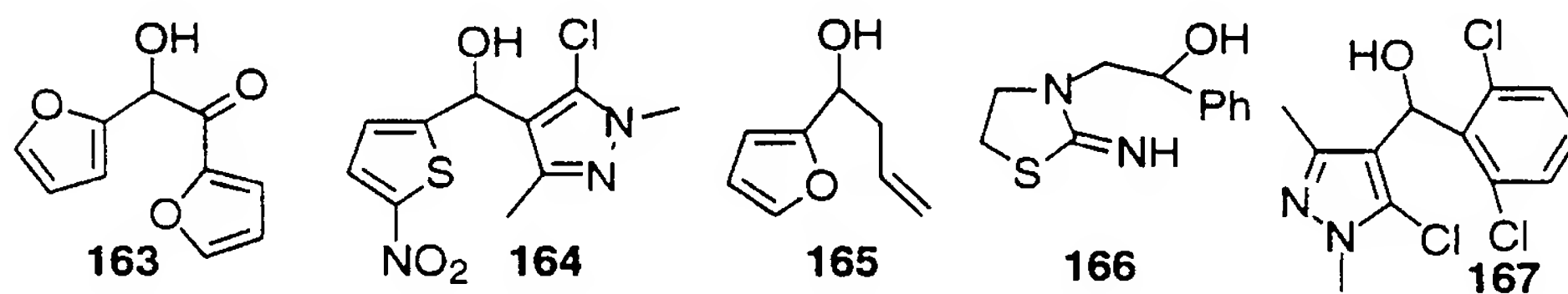




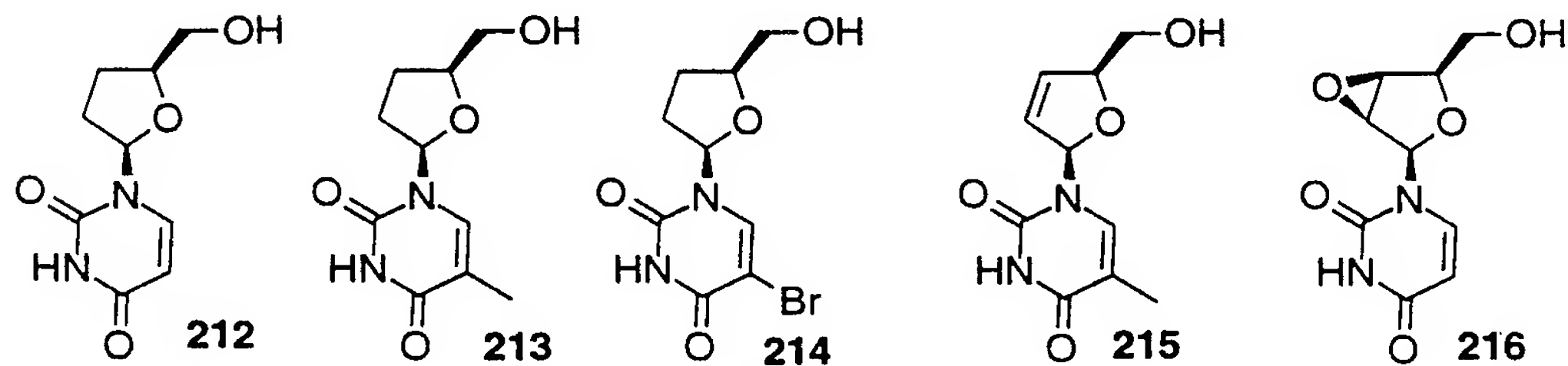
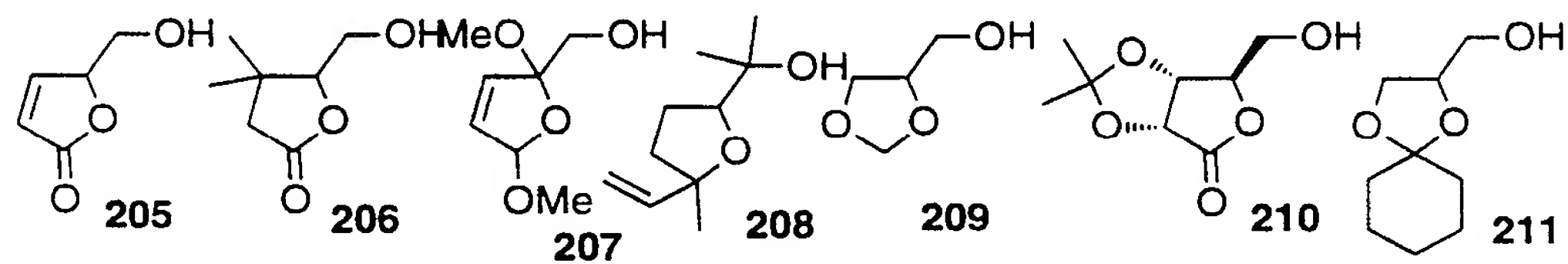
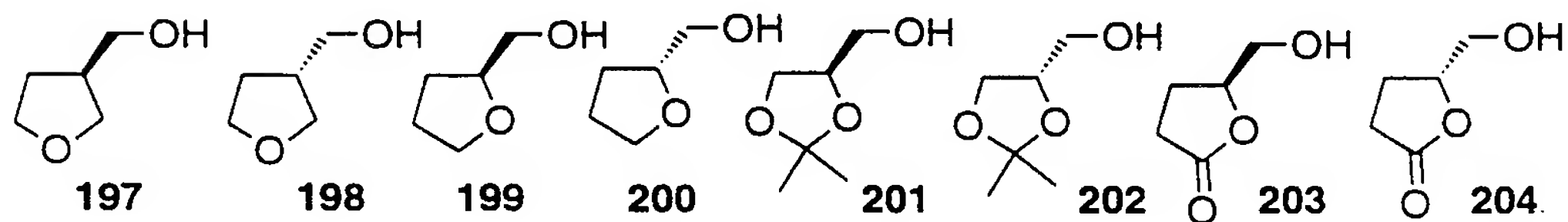
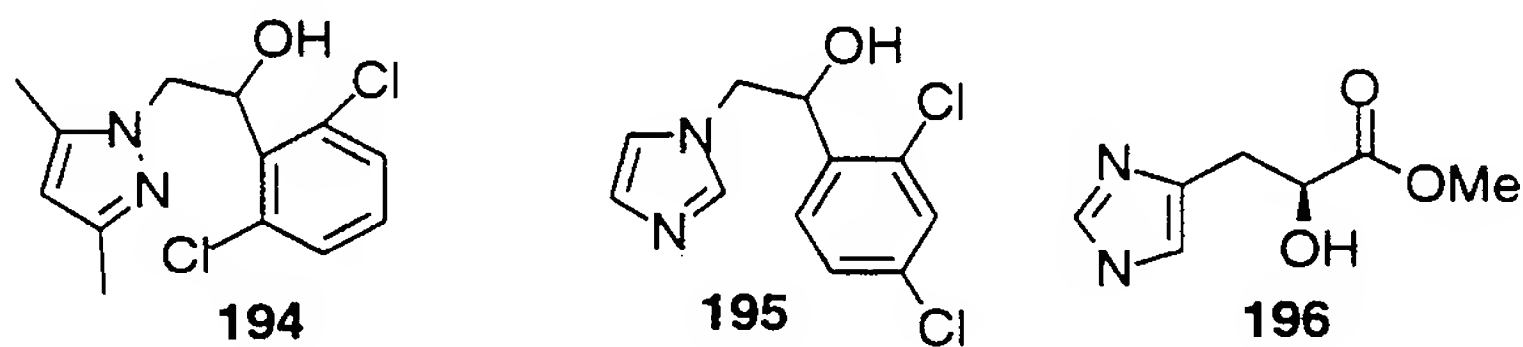
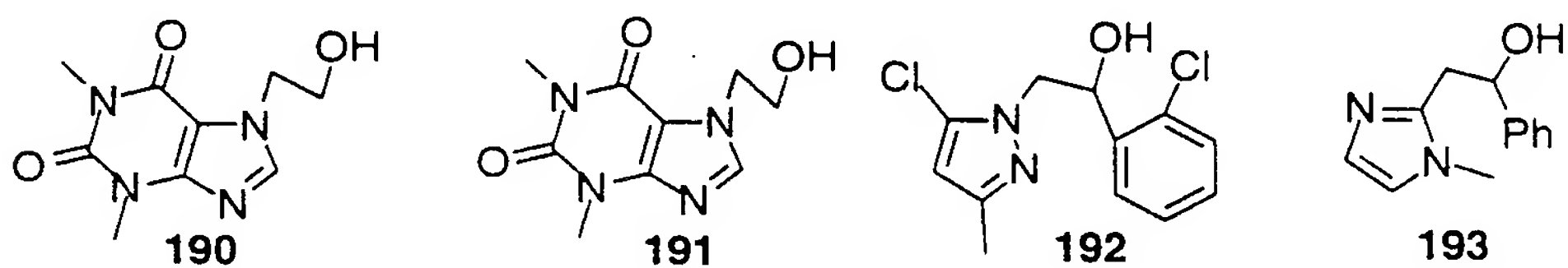
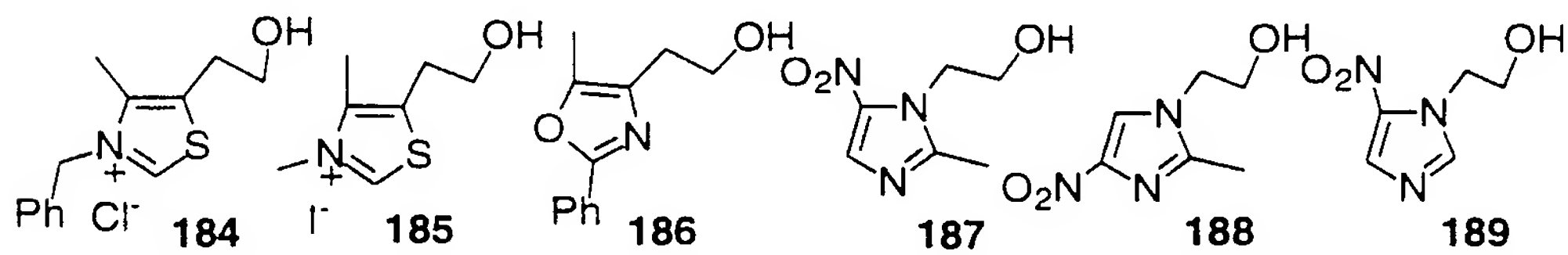
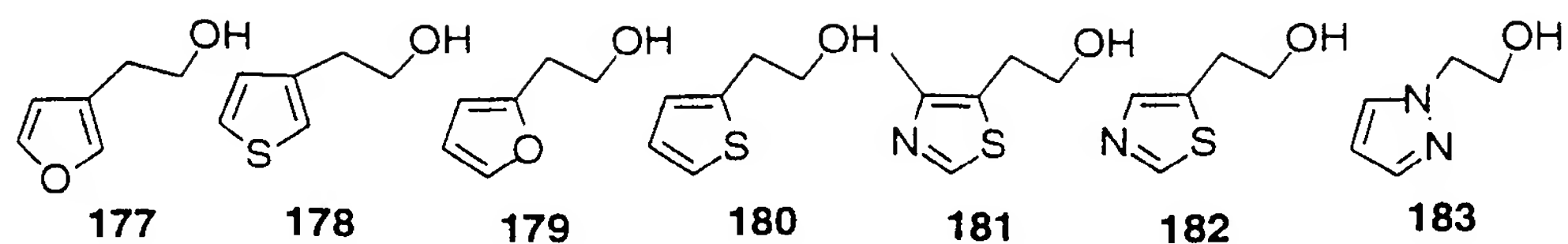
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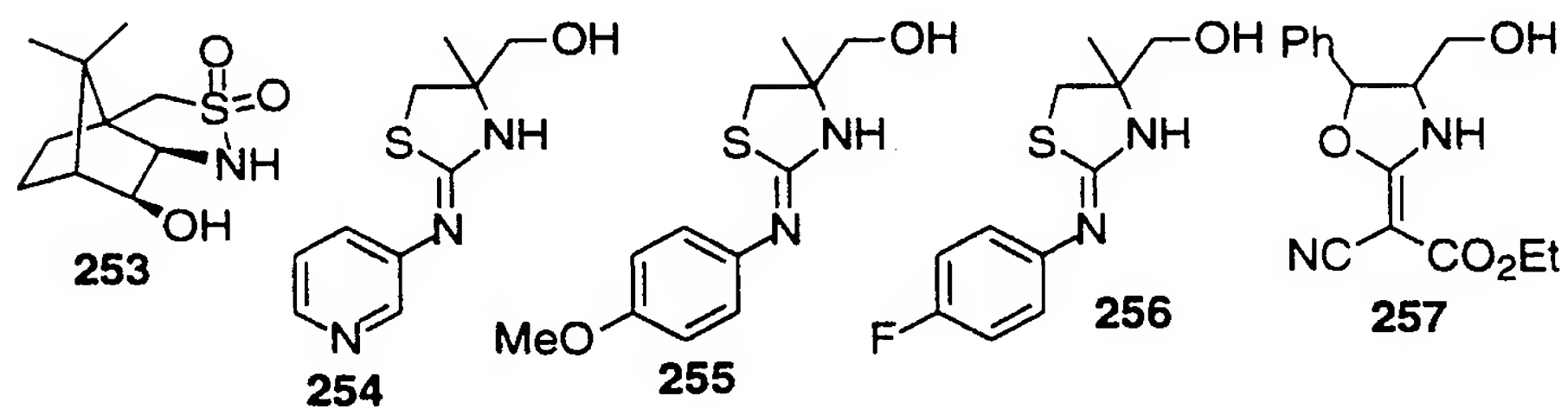
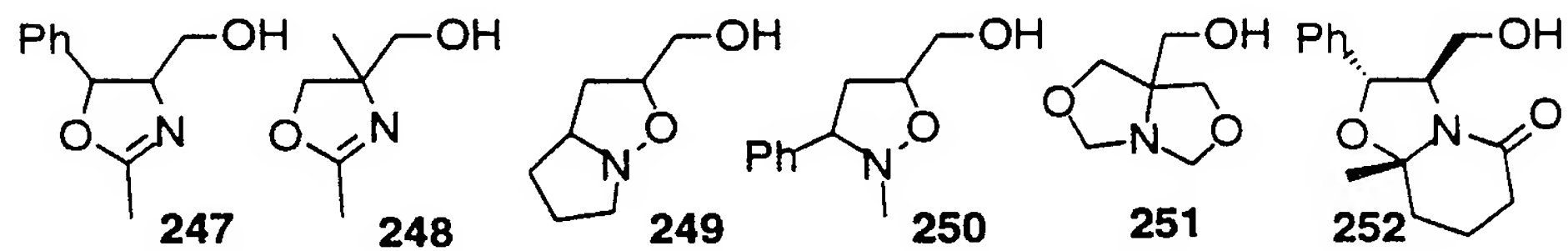
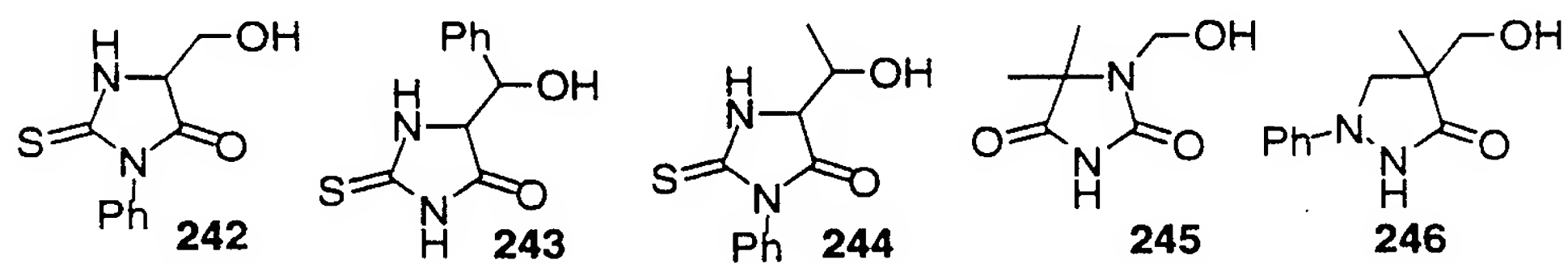
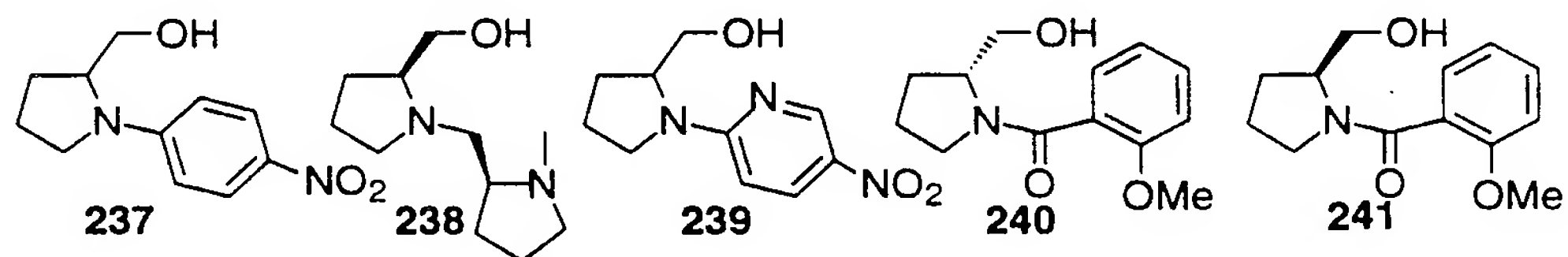
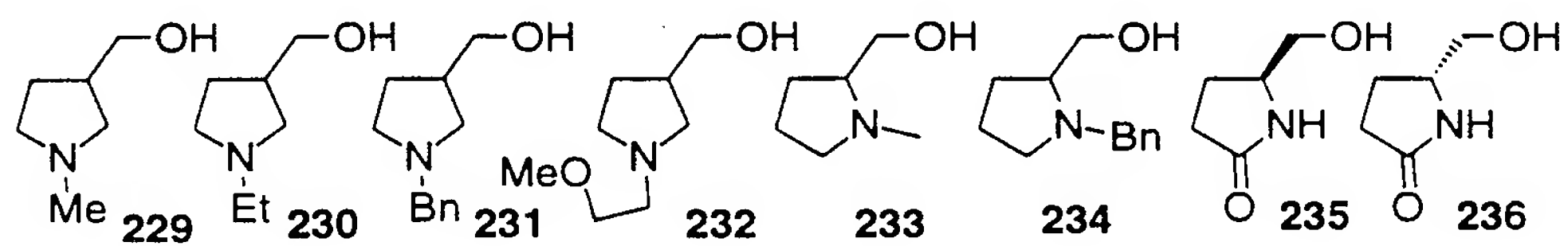
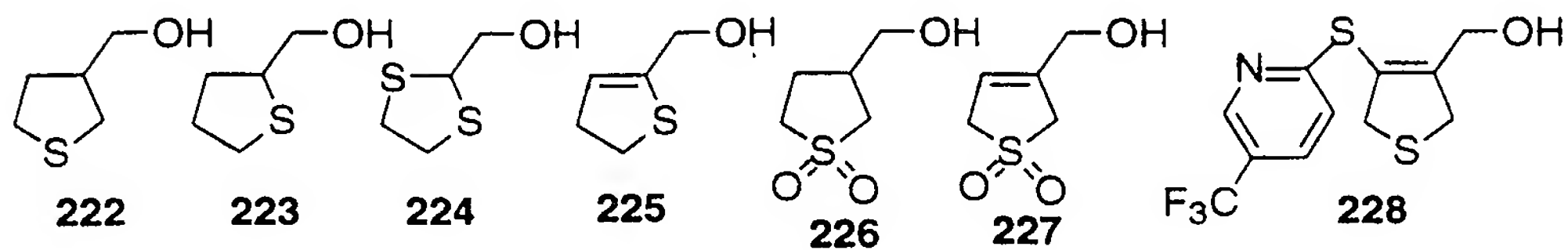
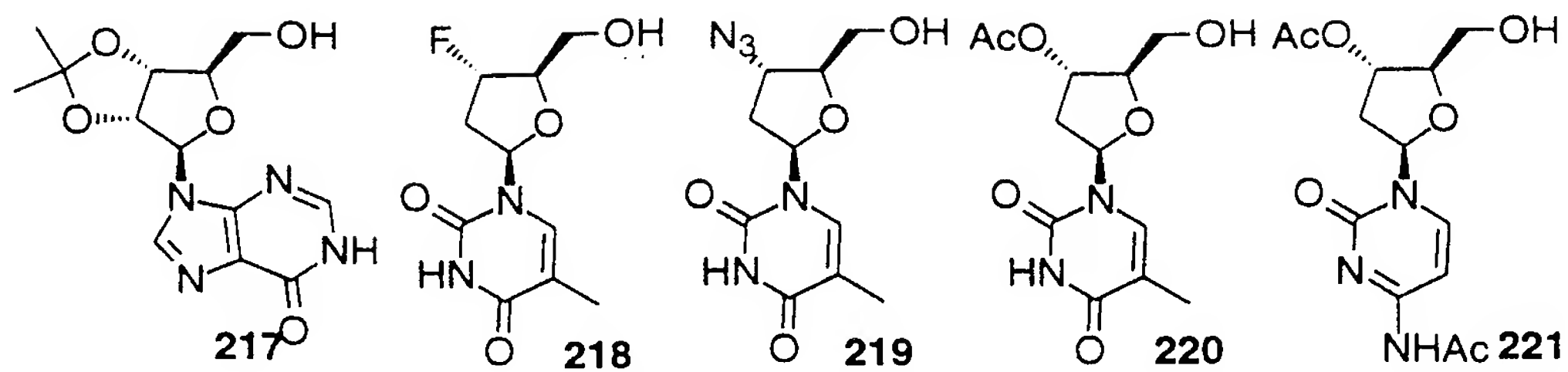
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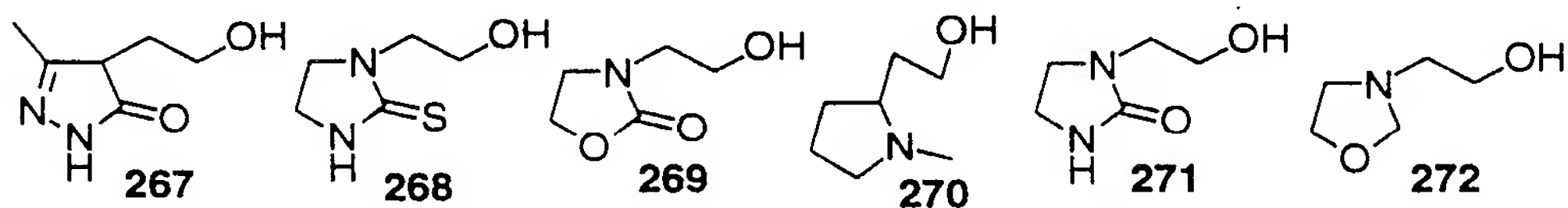
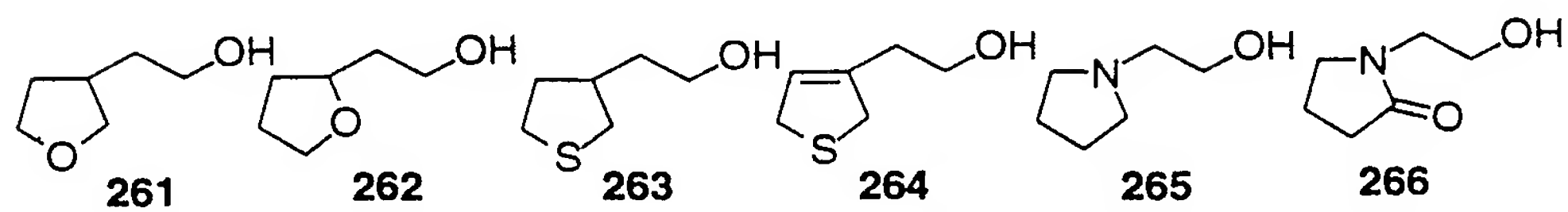
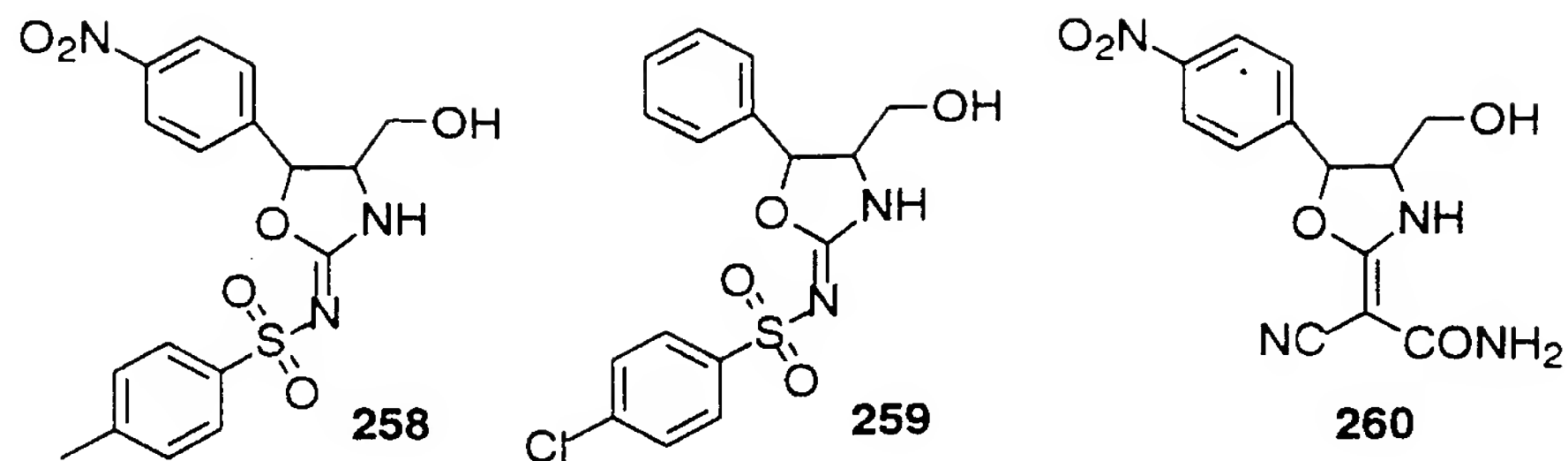


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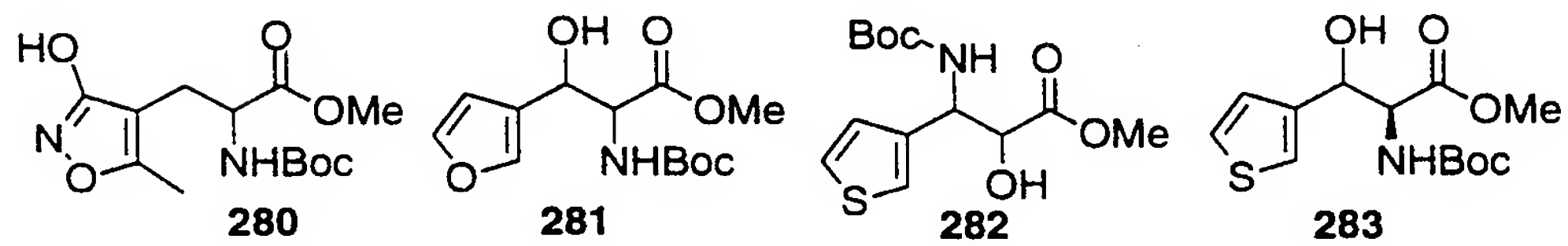
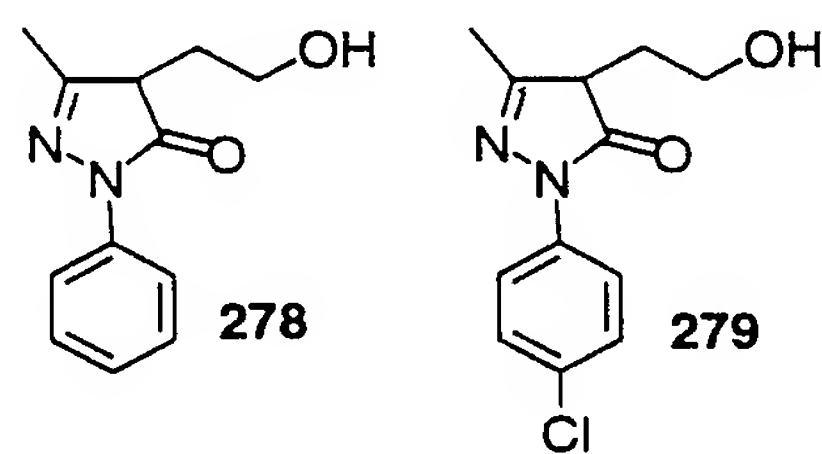
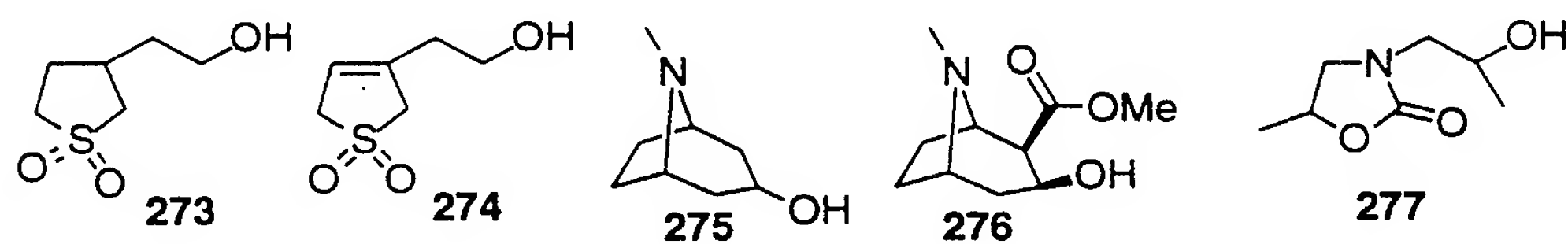
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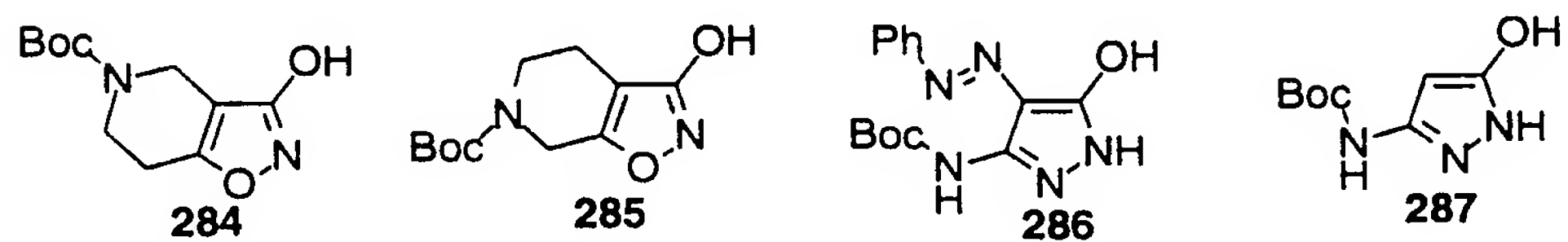
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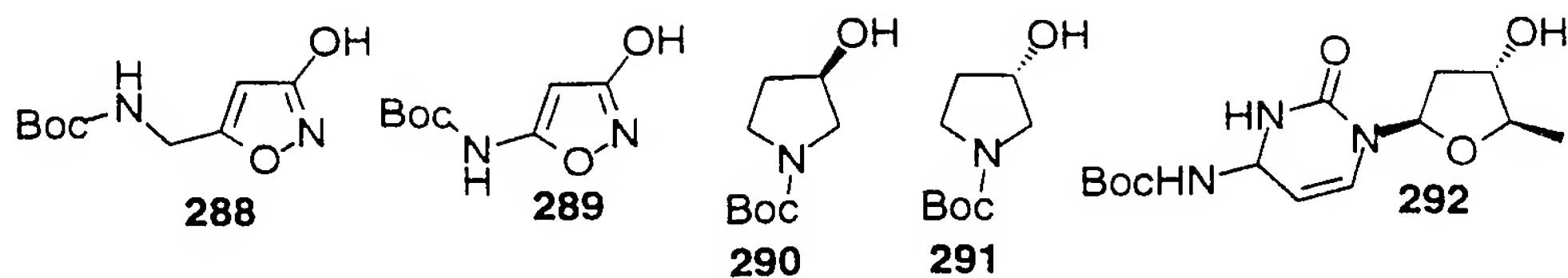


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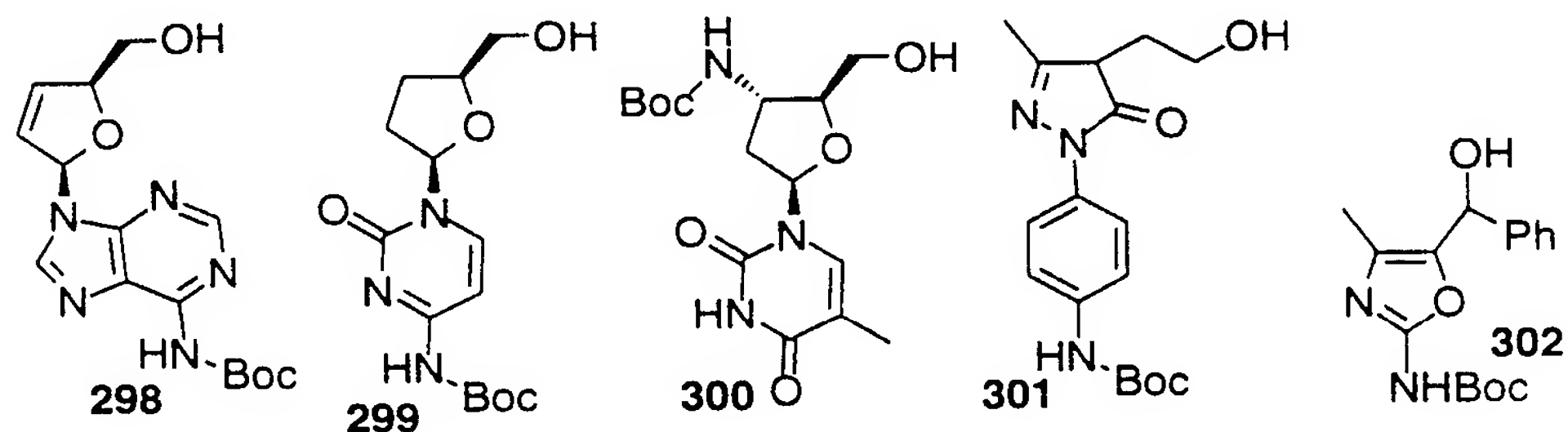
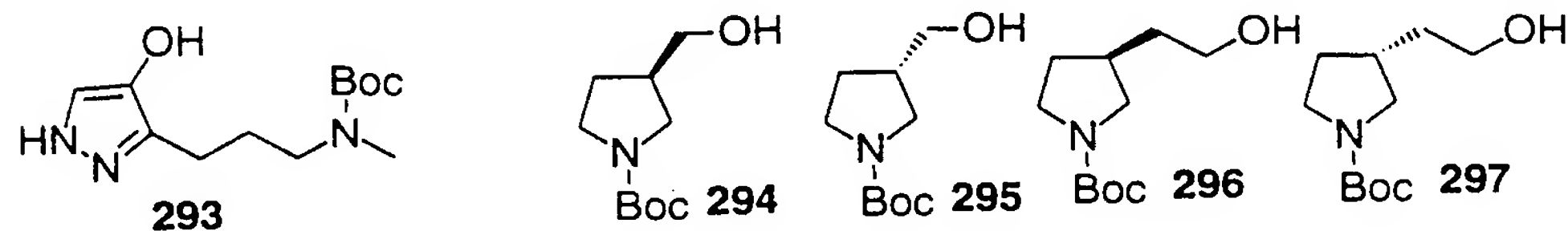


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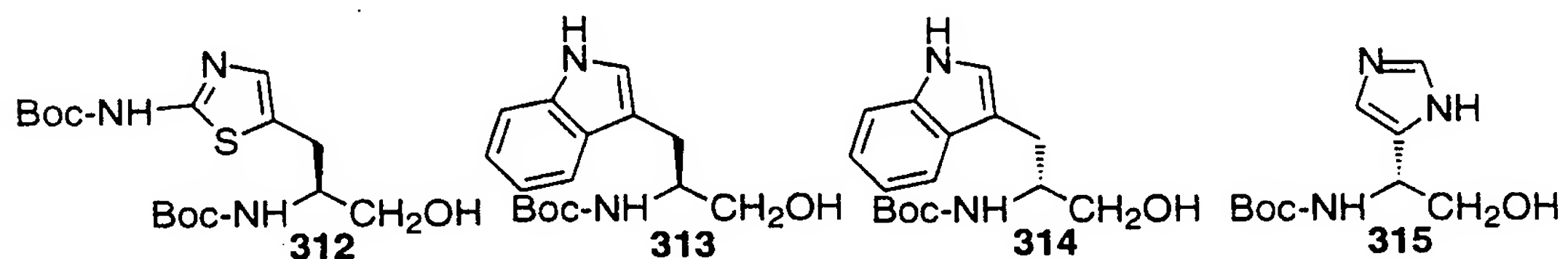
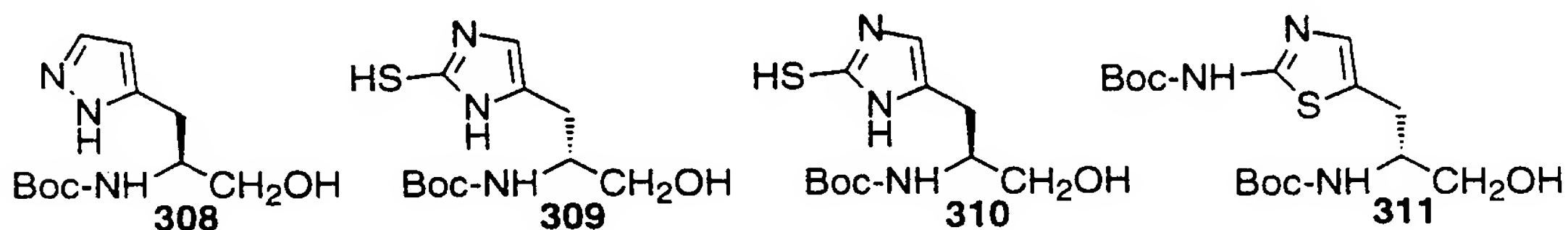
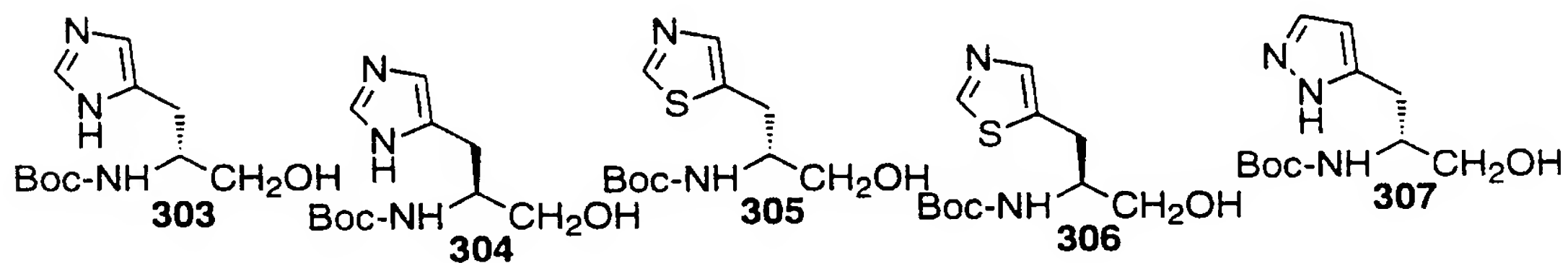




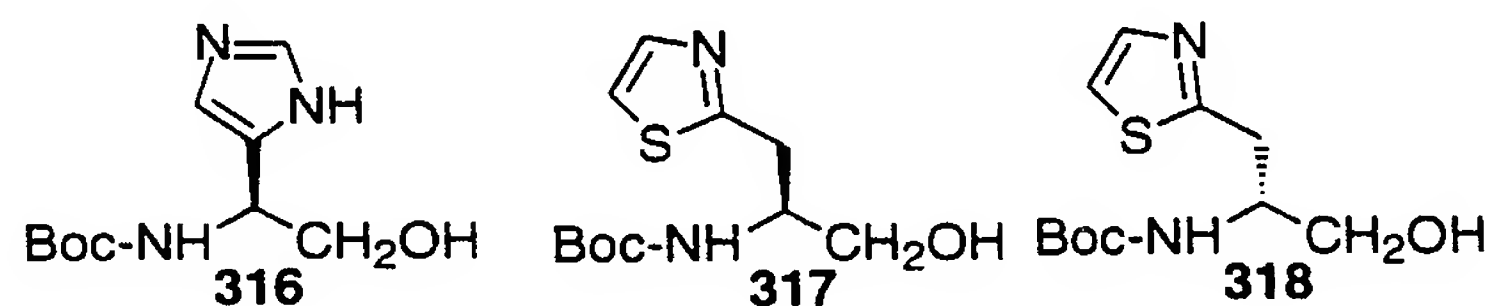
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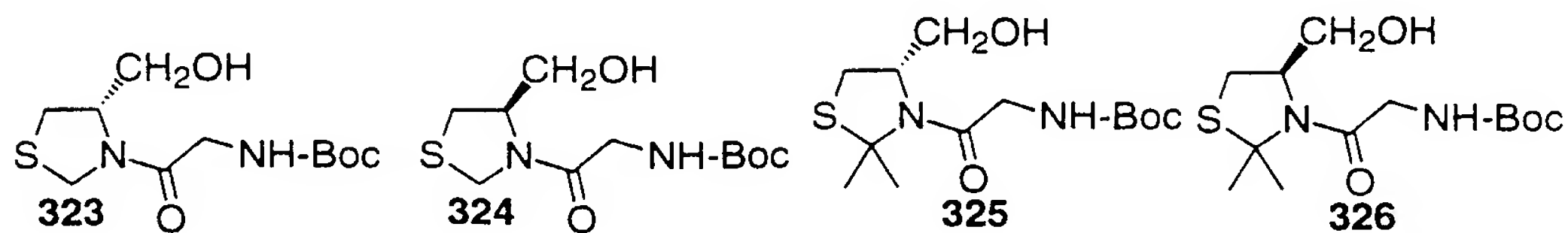
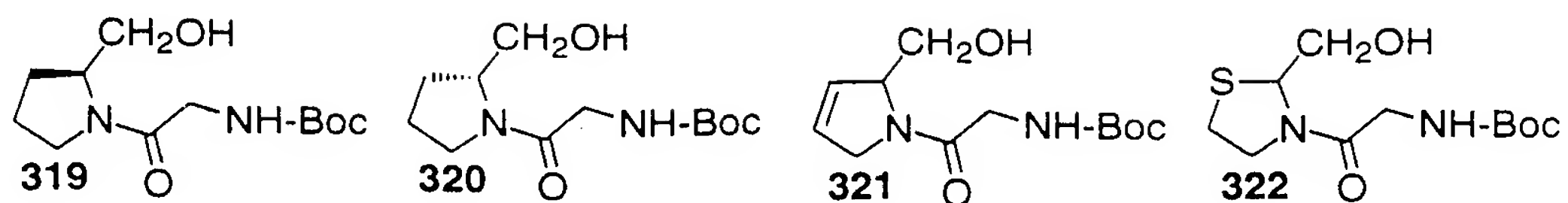


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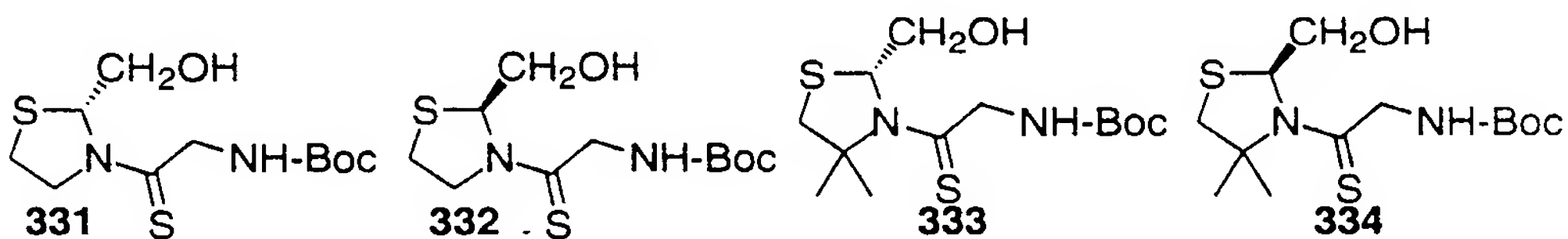
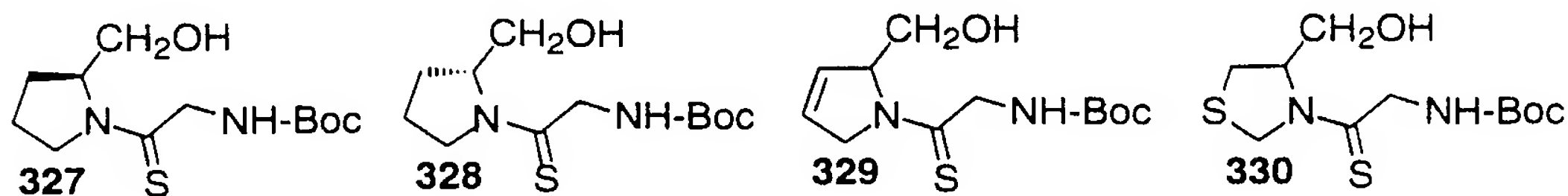


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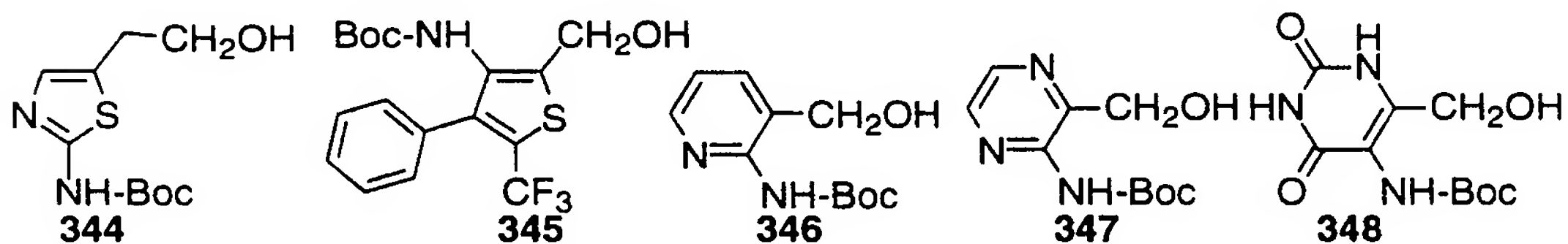
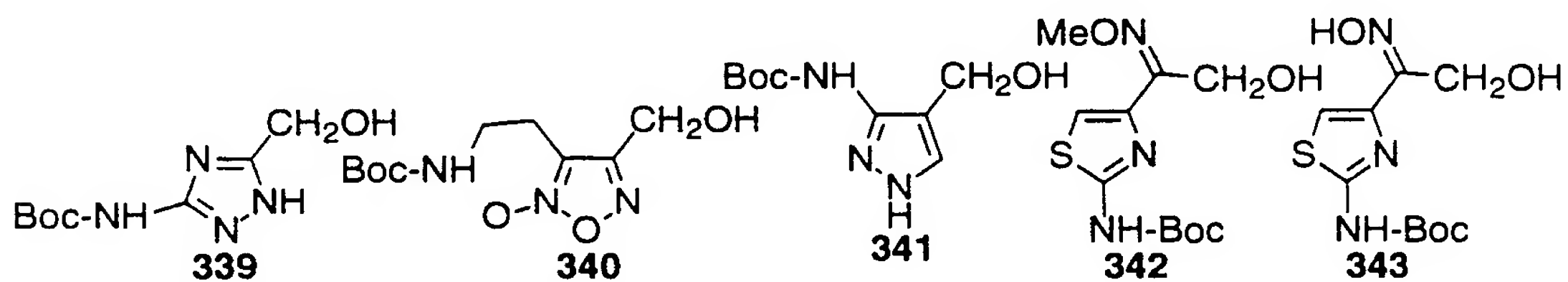
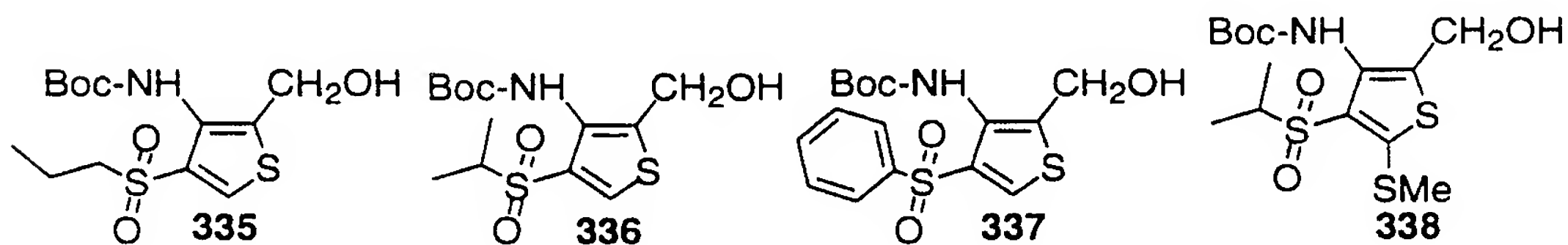




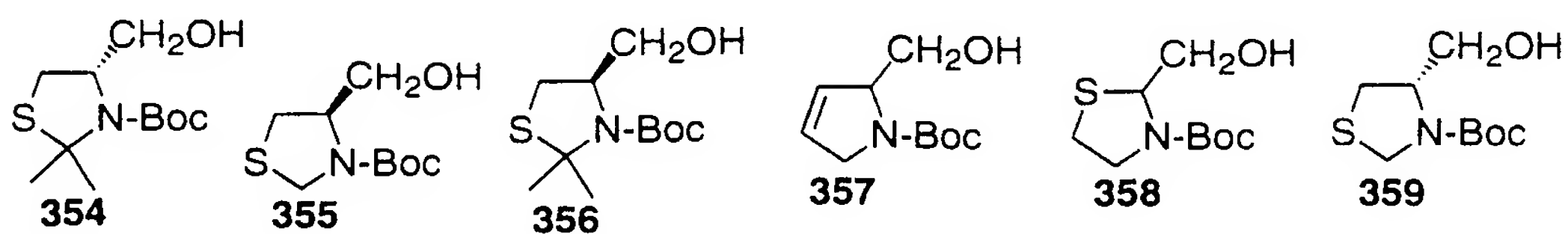
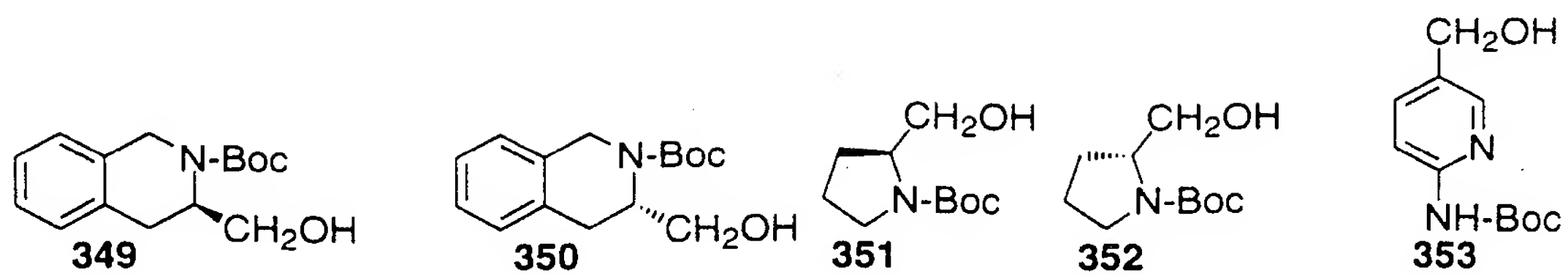
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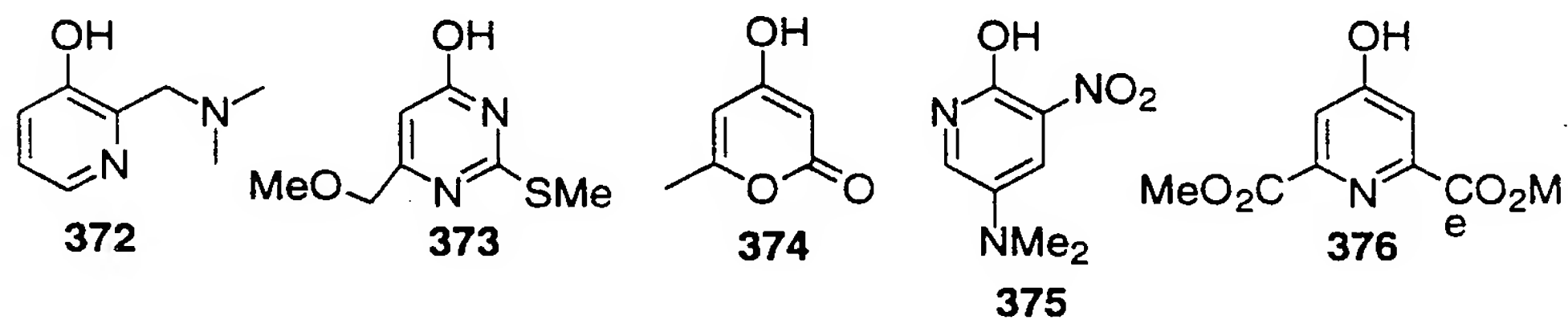
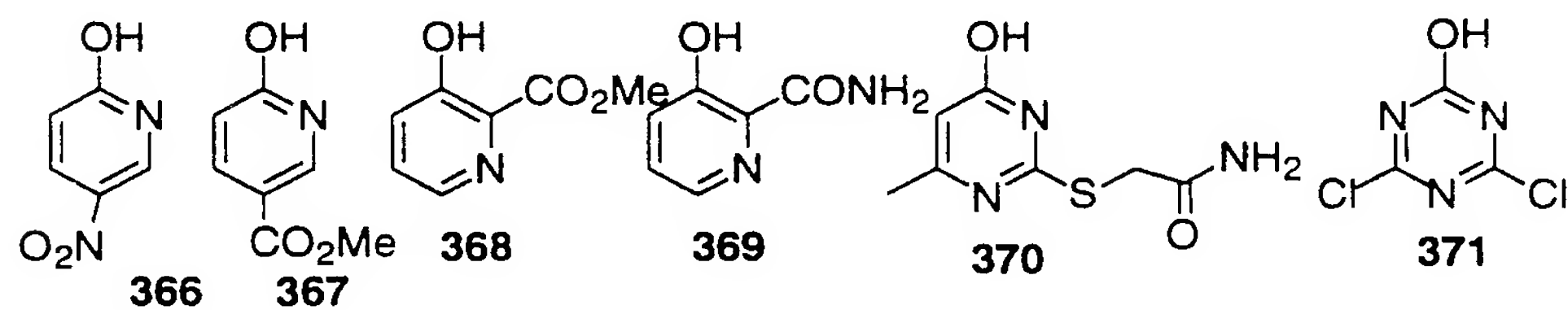
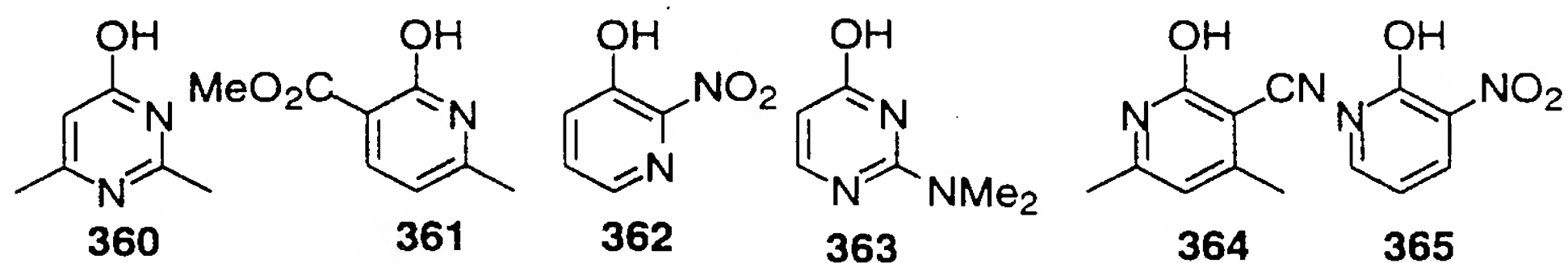
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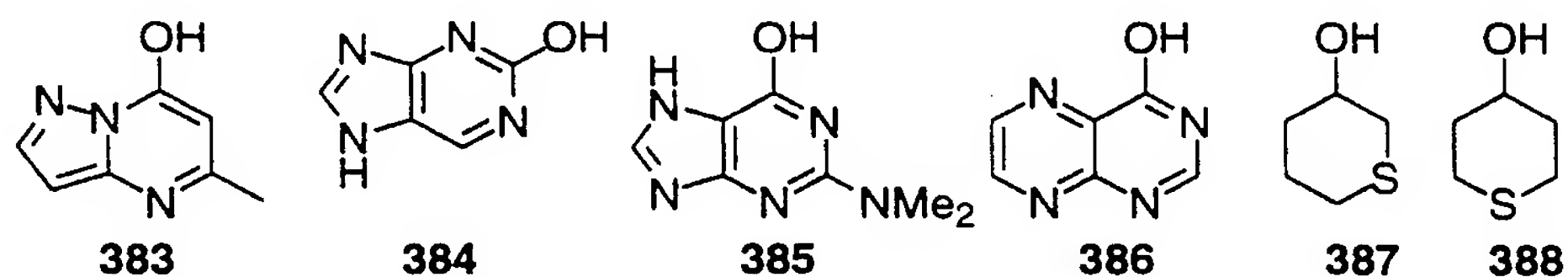
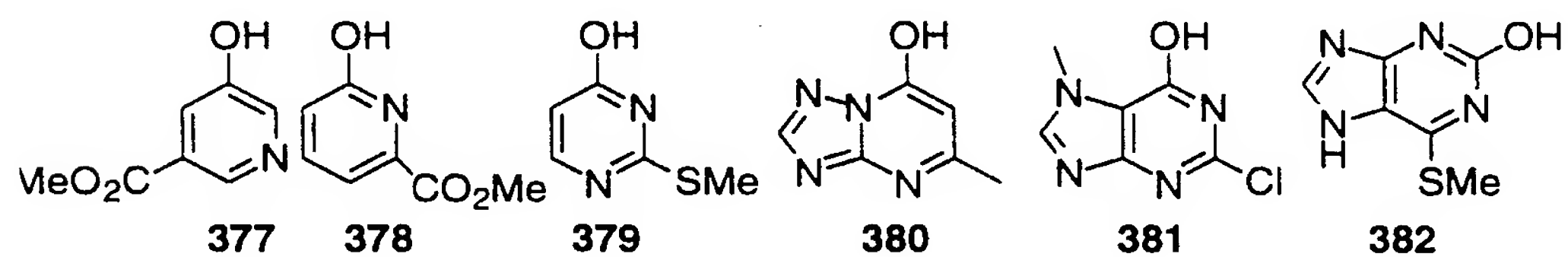
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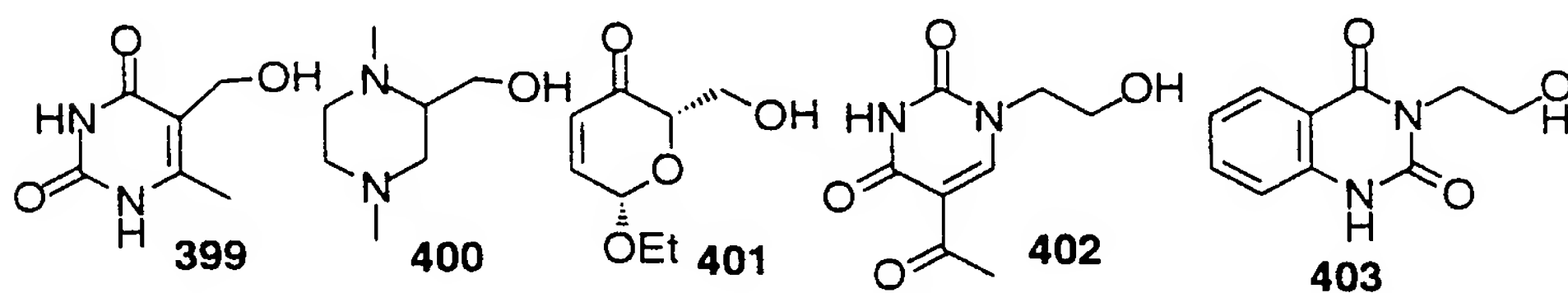
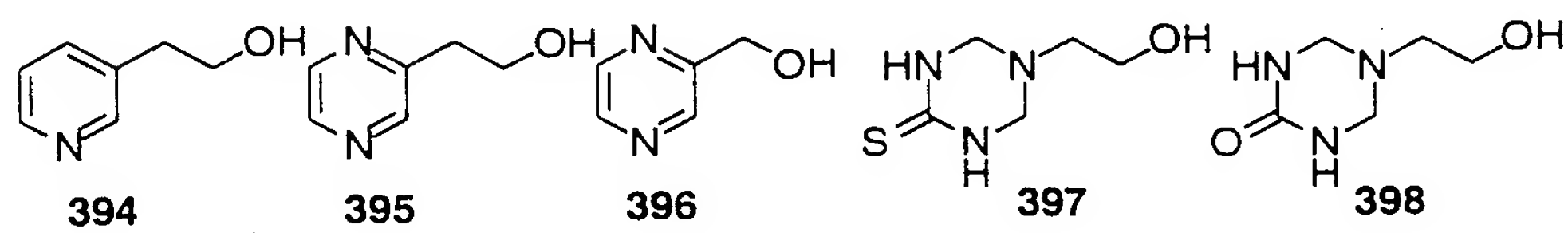
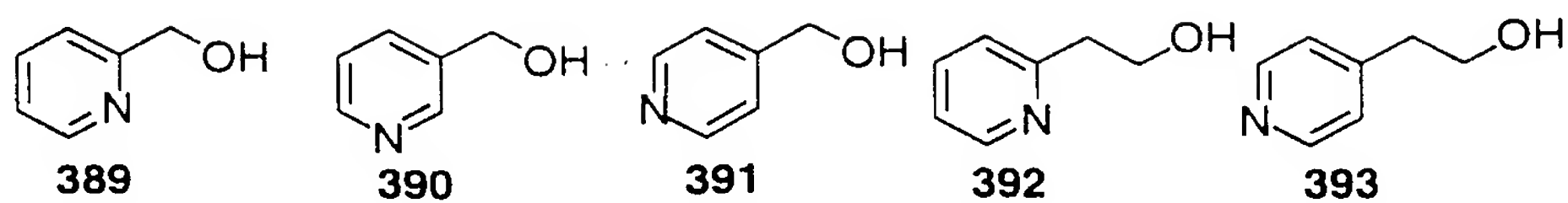
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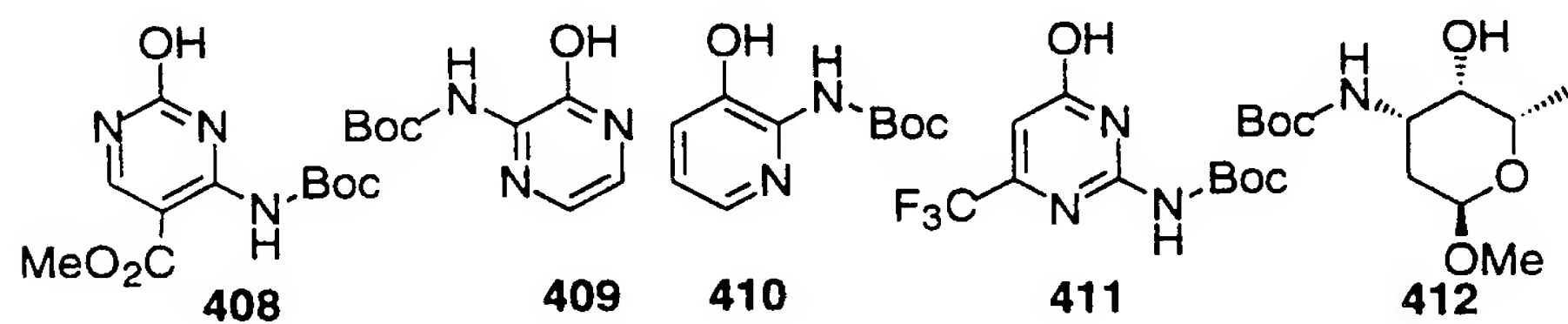
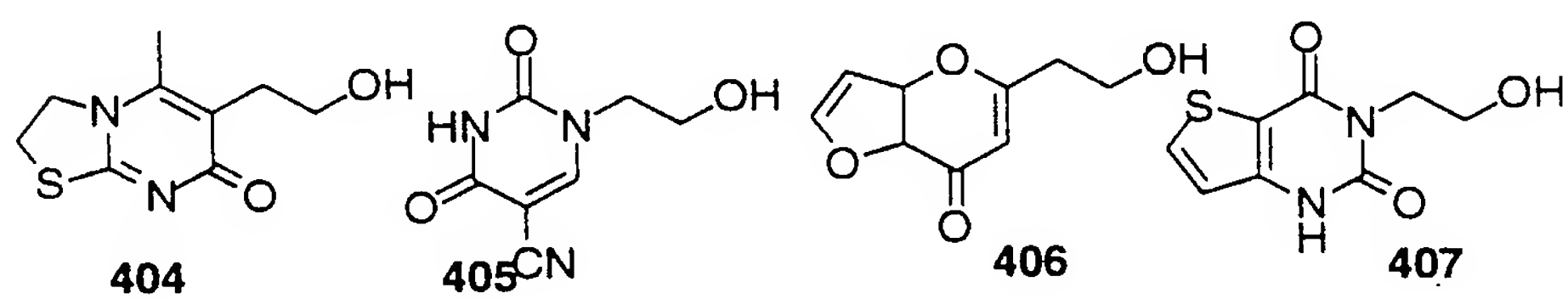
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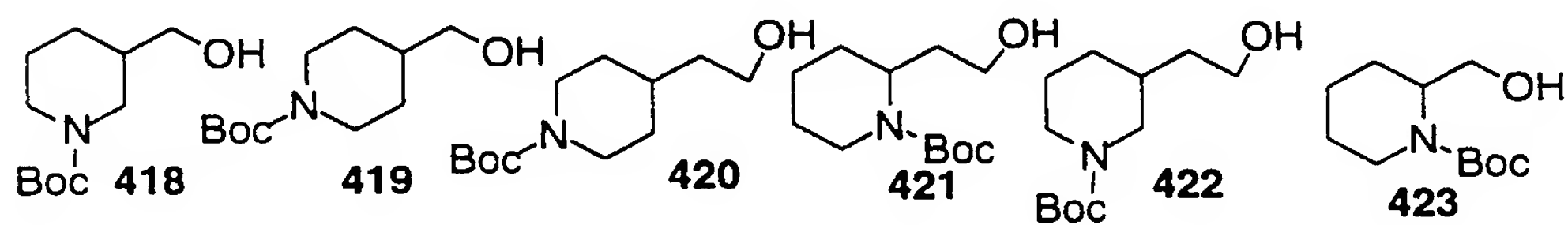
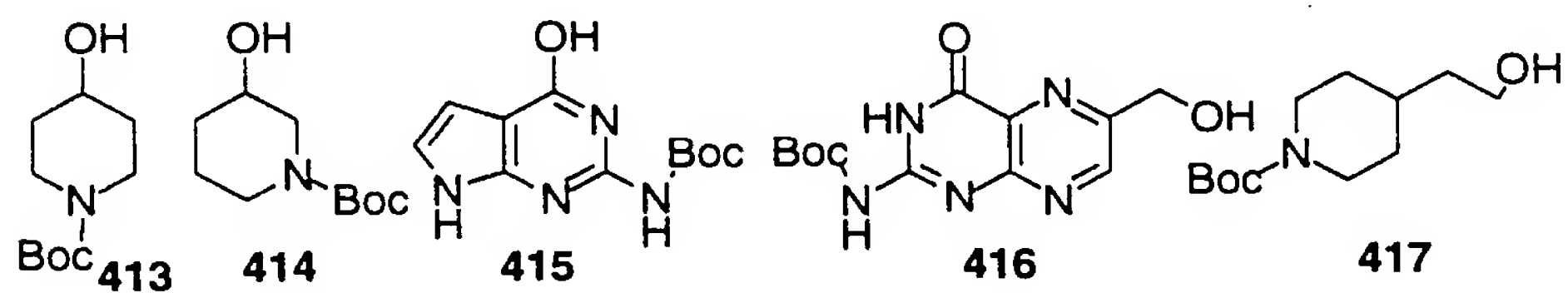
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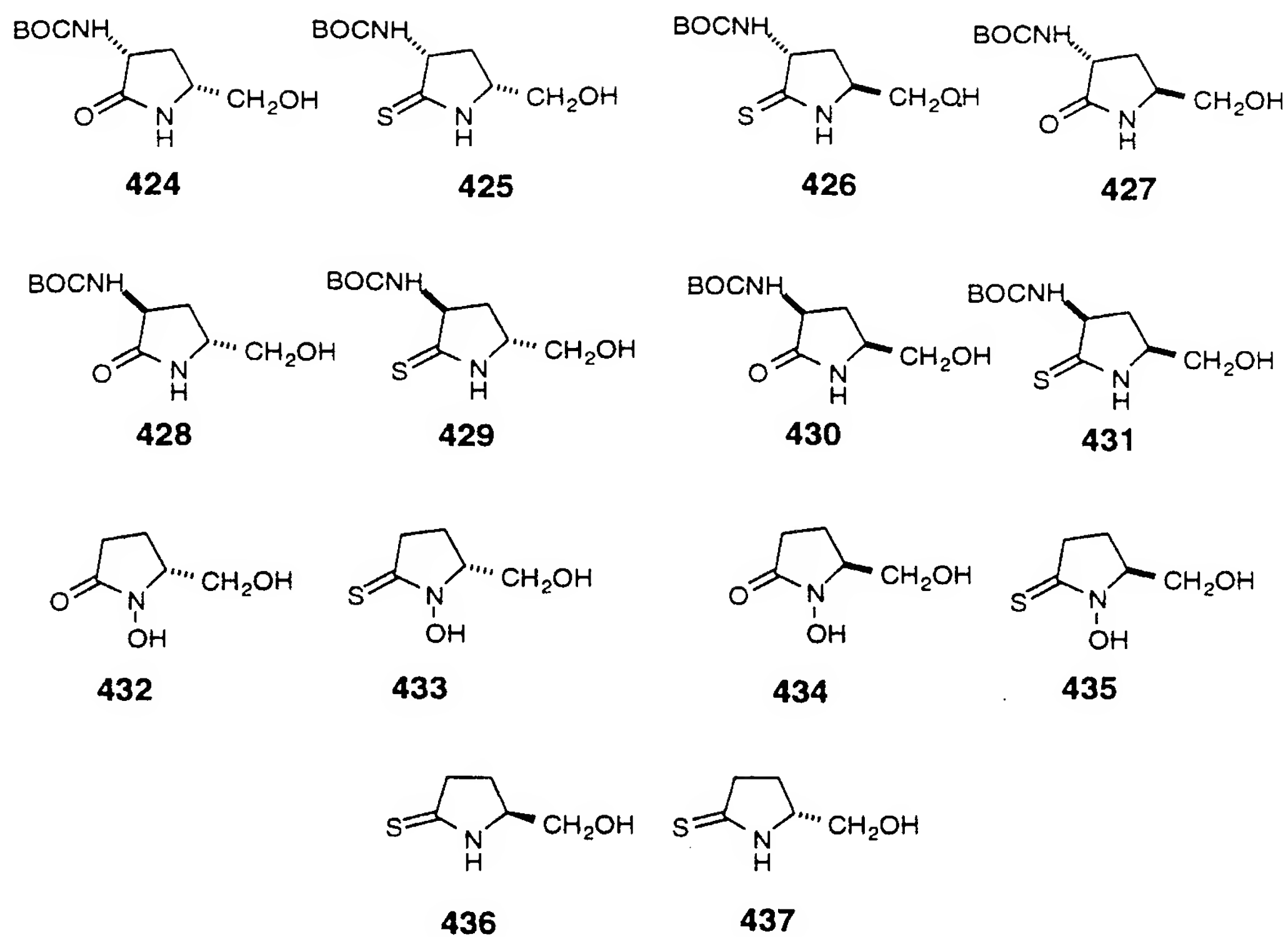
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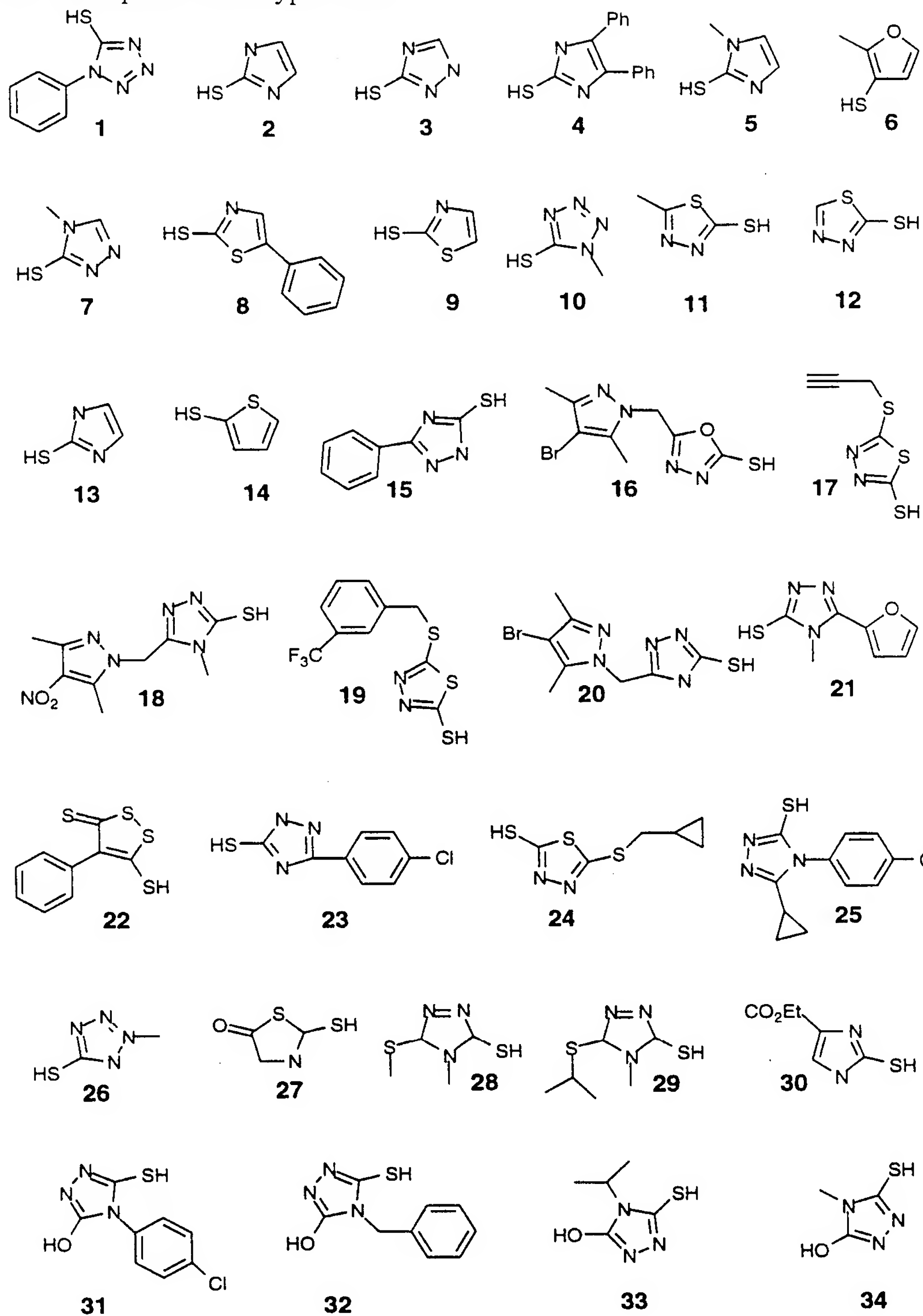


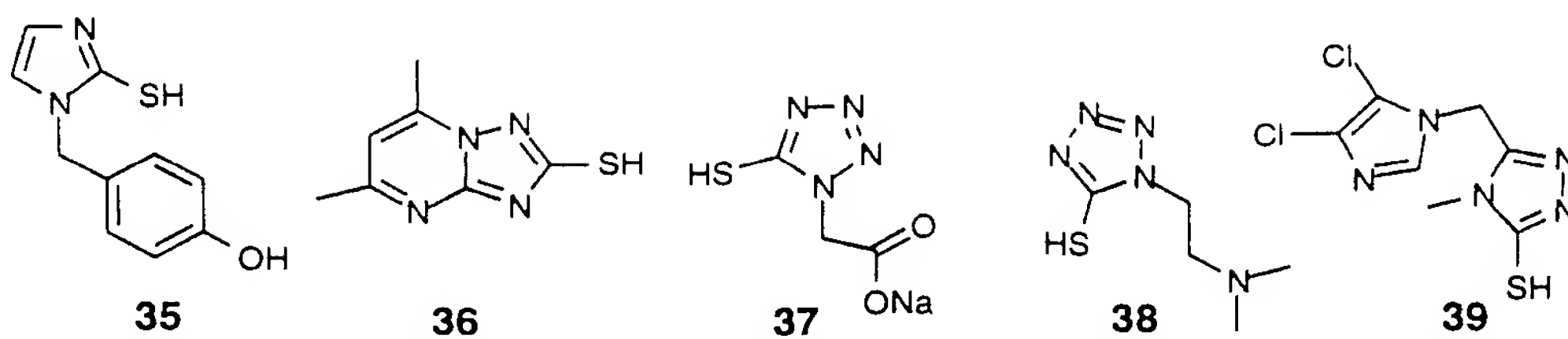
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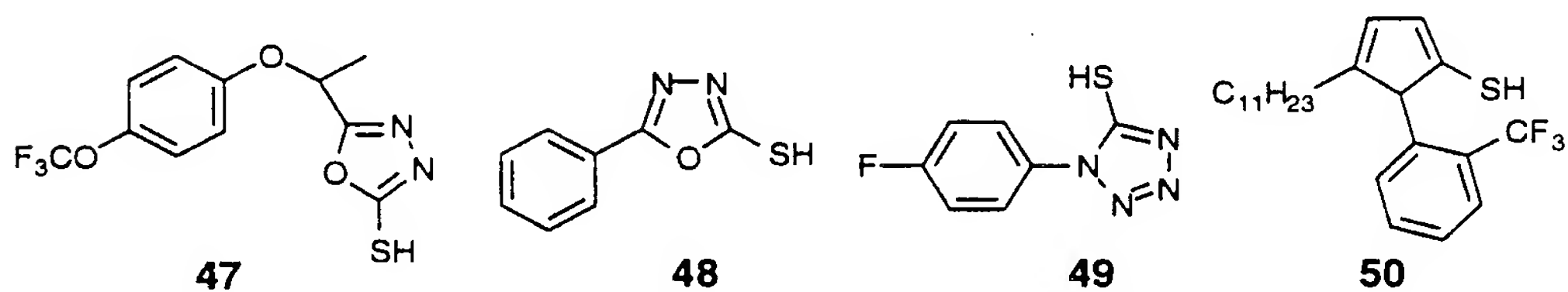
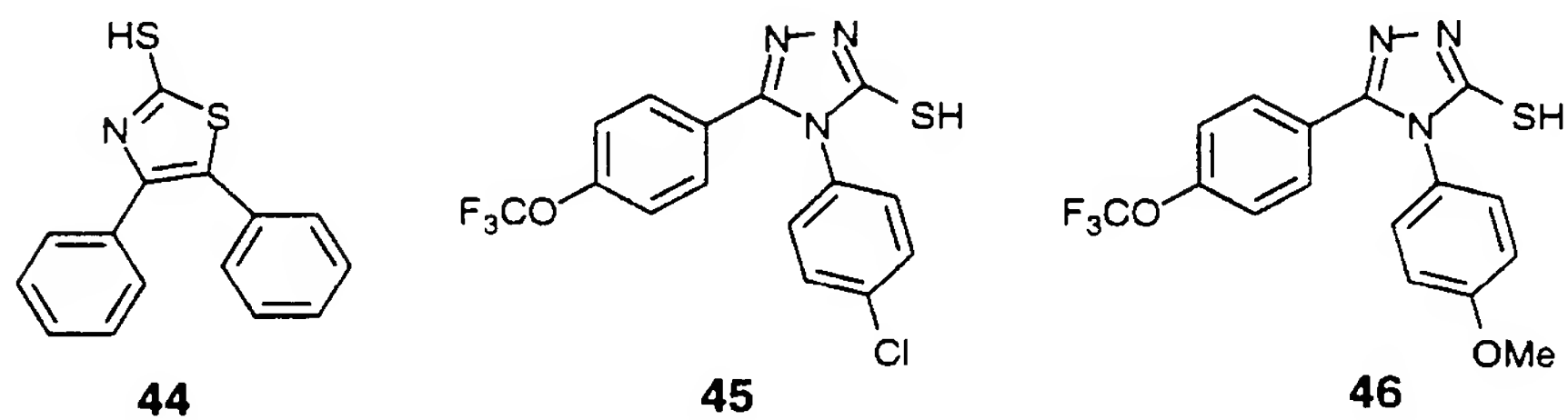
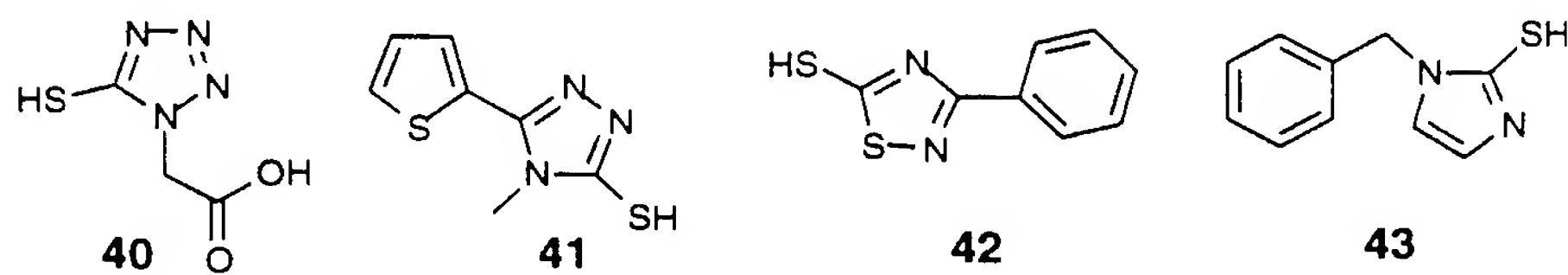
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Table 16. Mercaptans of the type A-SH

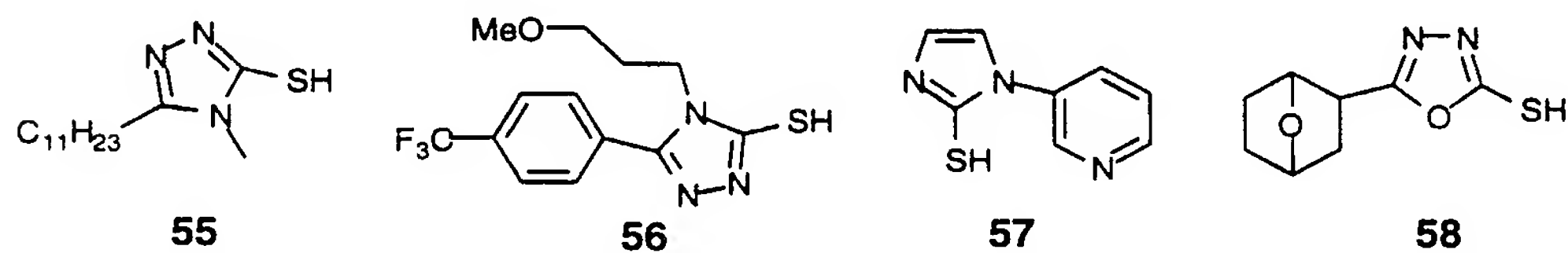
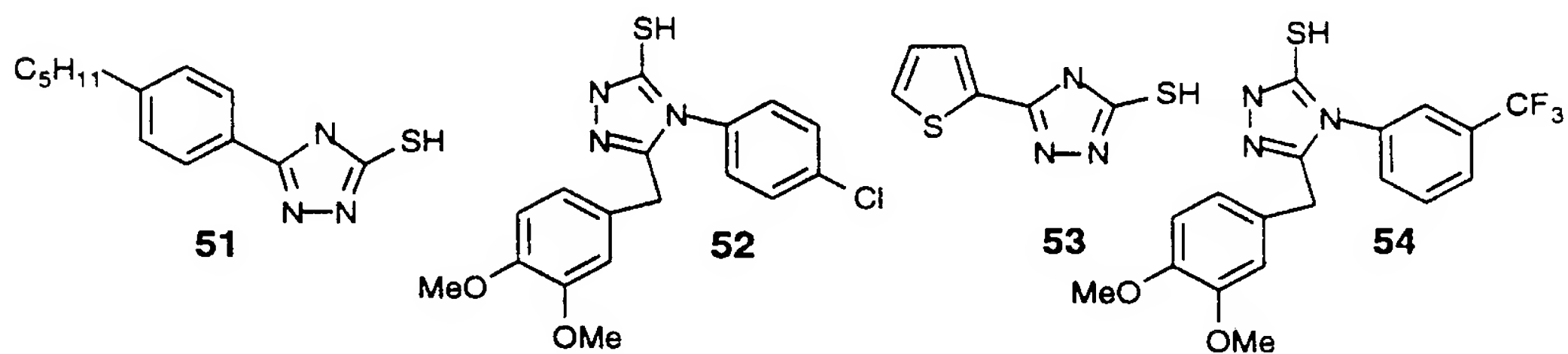




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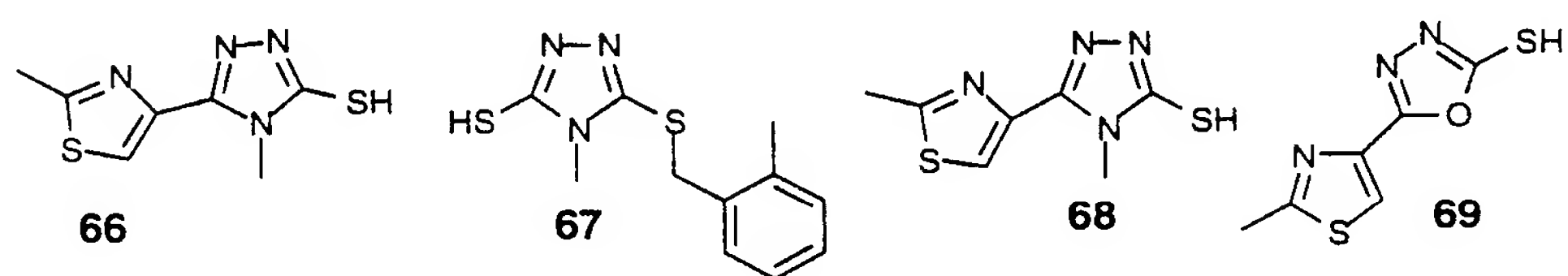
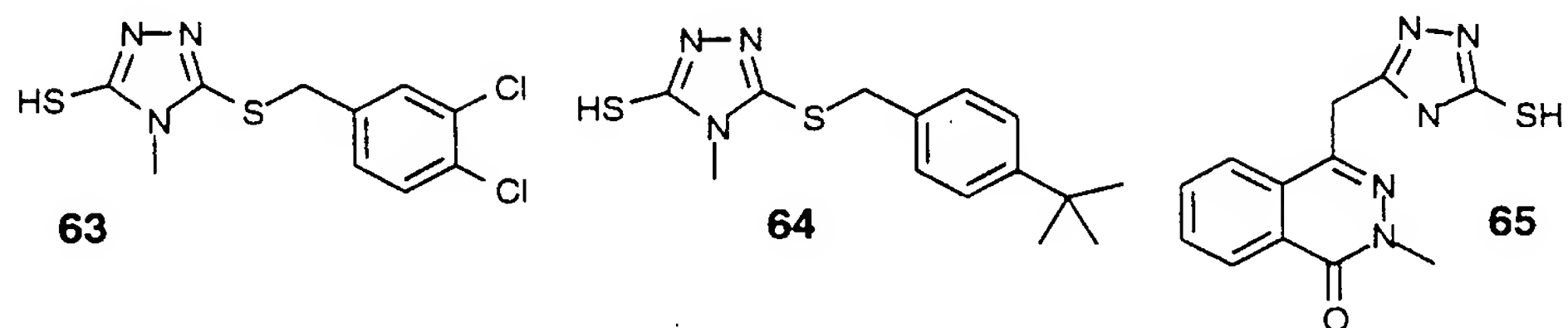
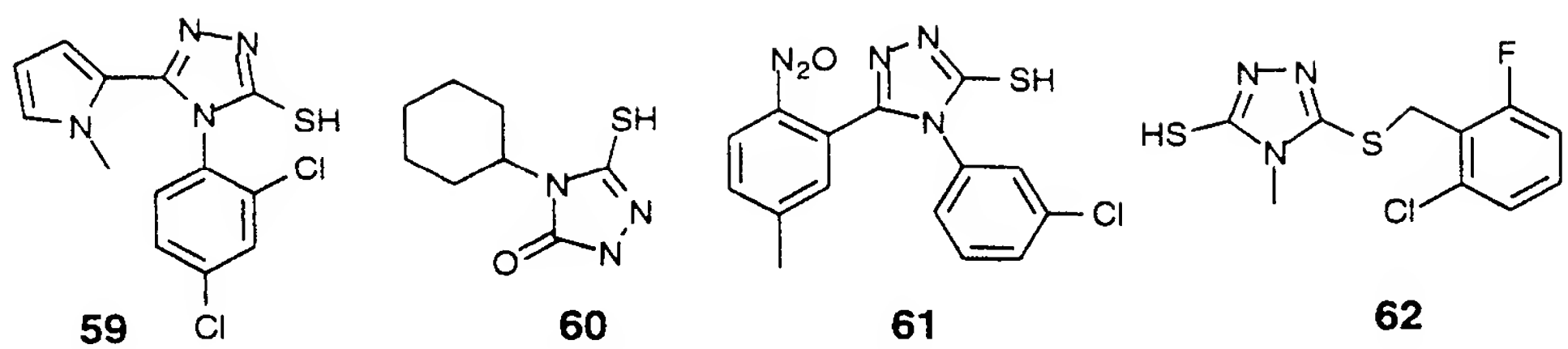


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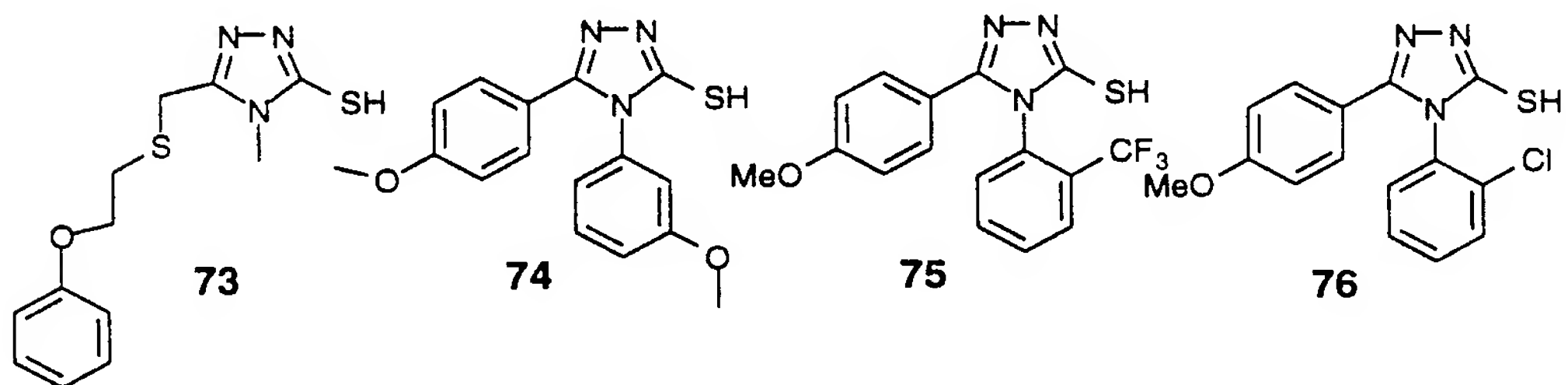
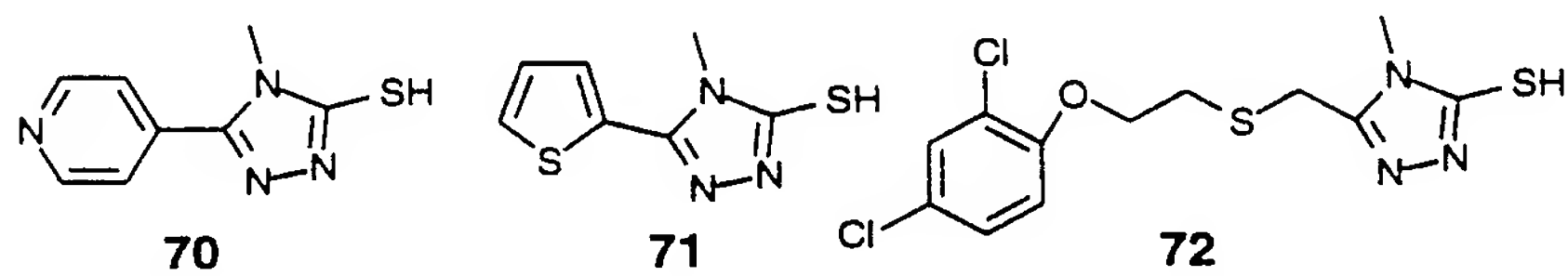


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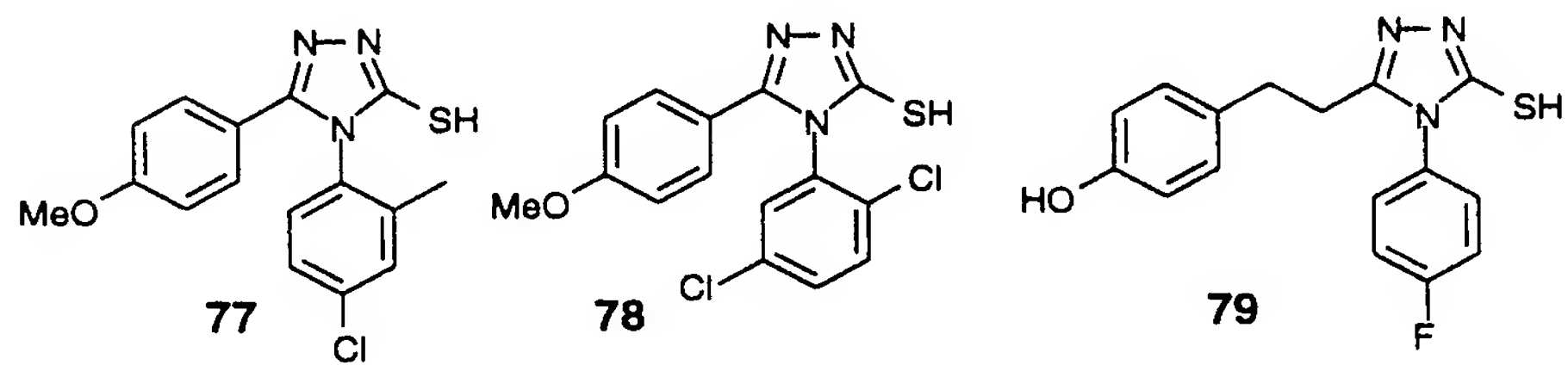


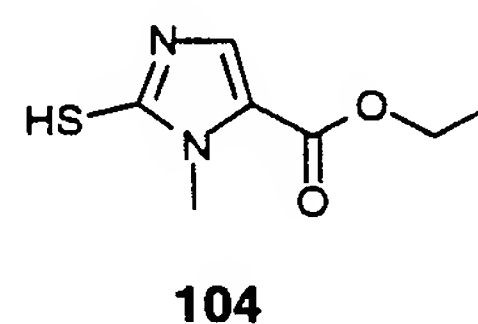
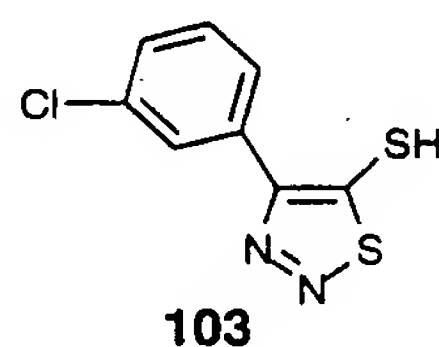
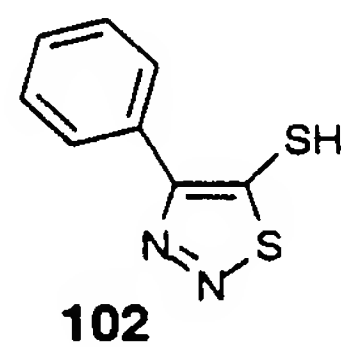
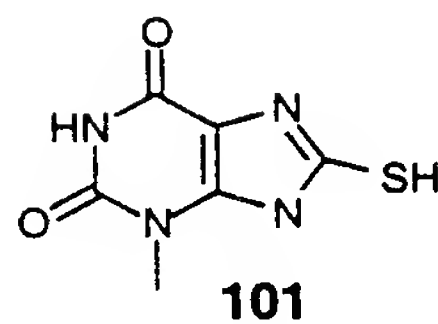
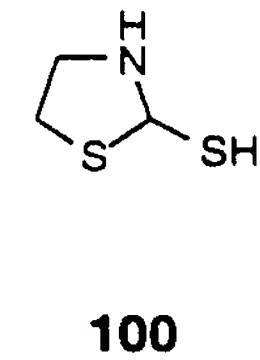
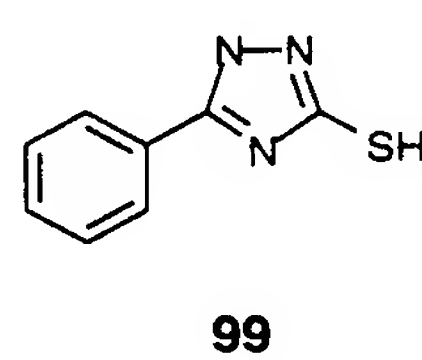
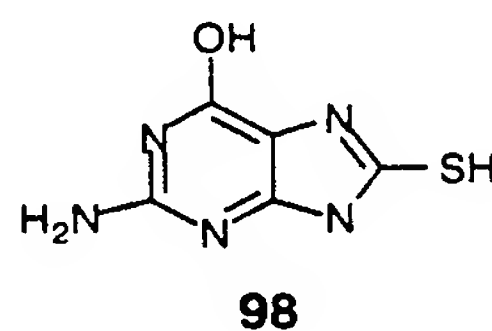
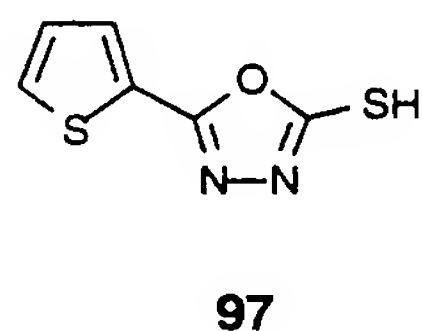
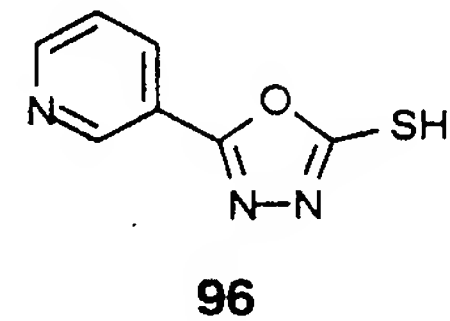
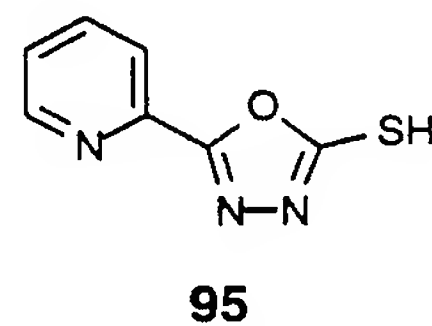
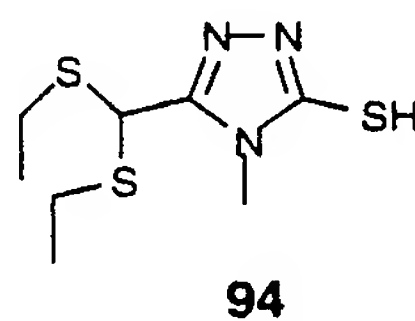
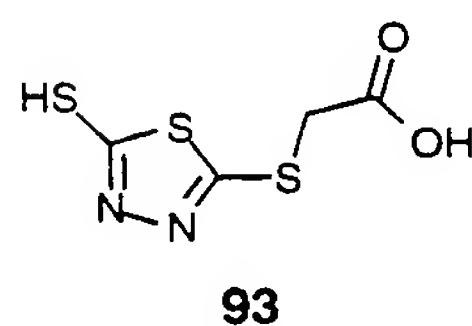
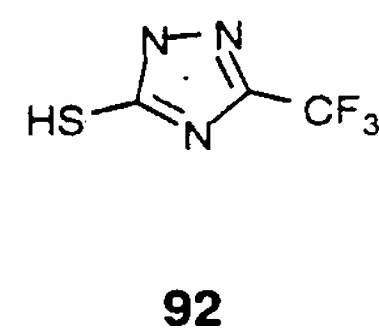
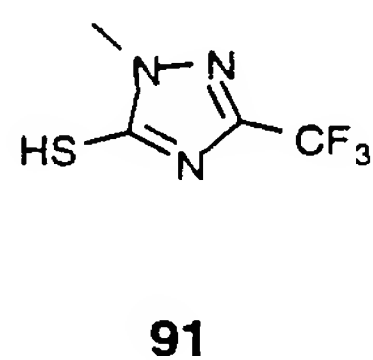
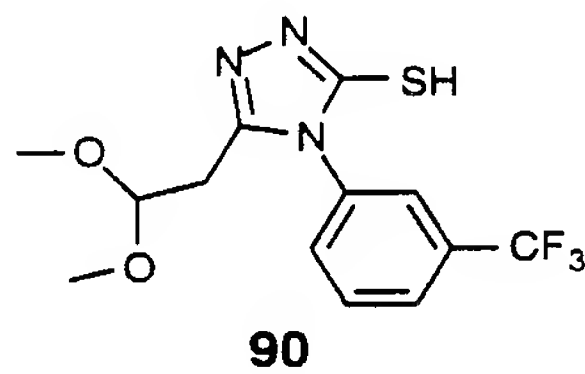
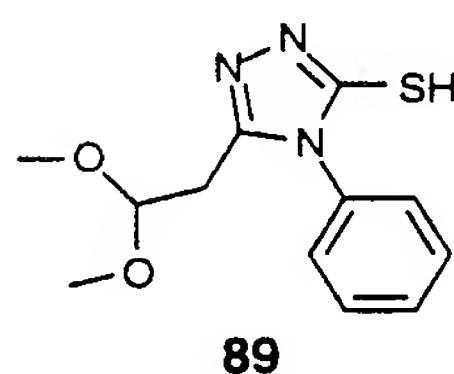
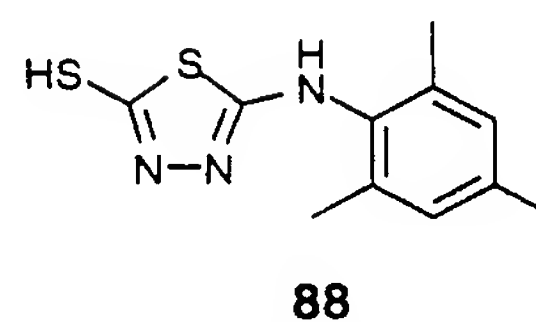
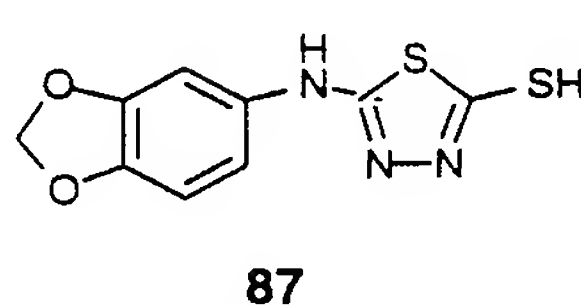
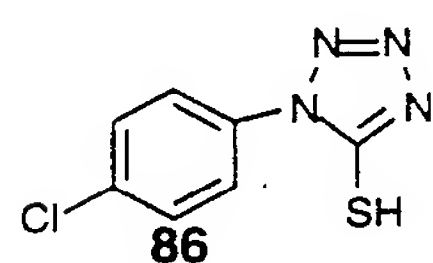
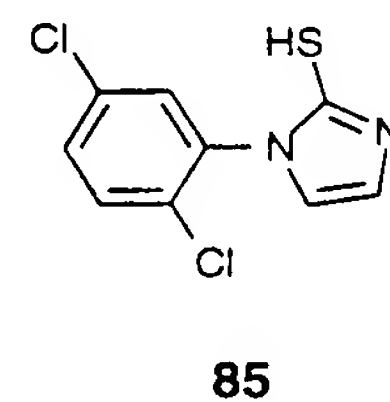
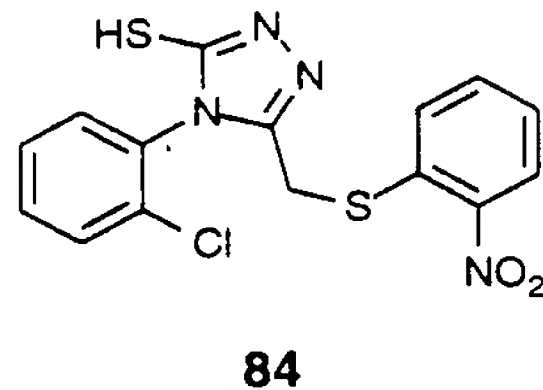
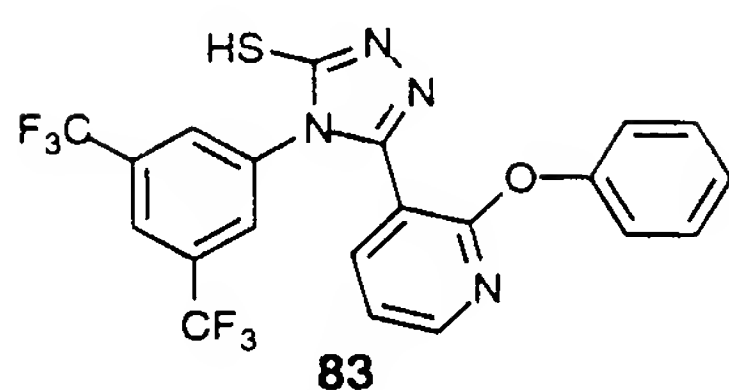
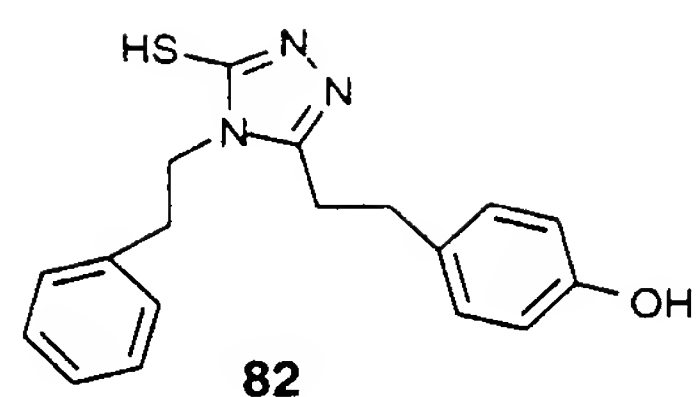
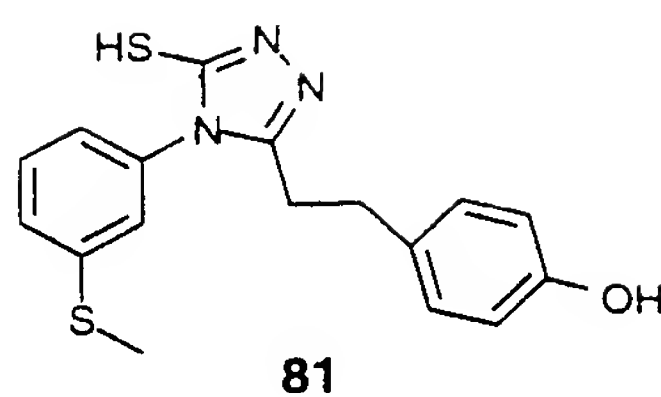
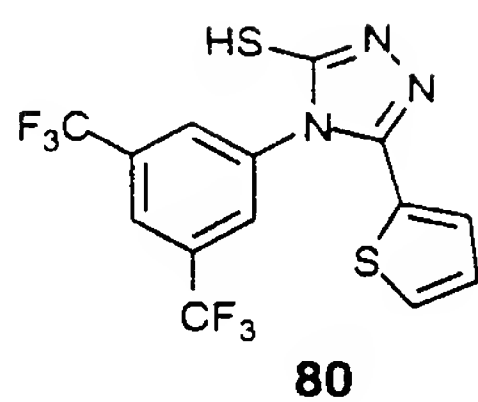


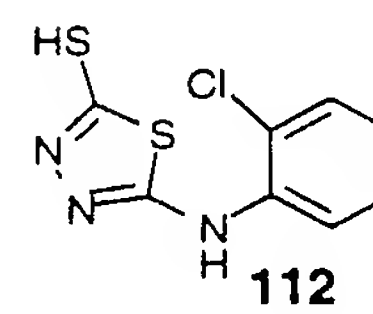
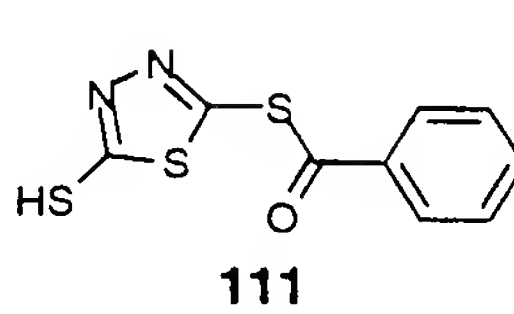
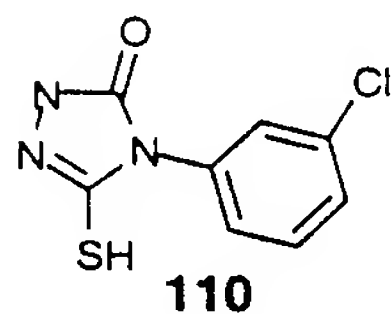
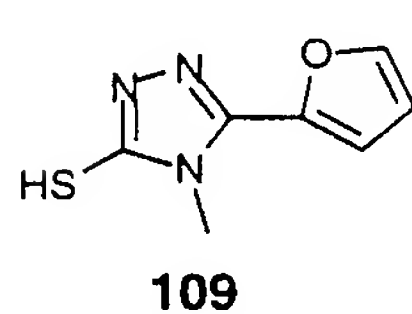
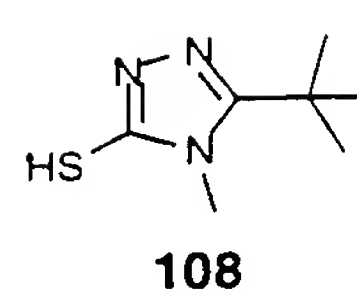
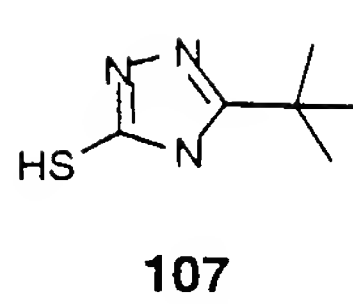
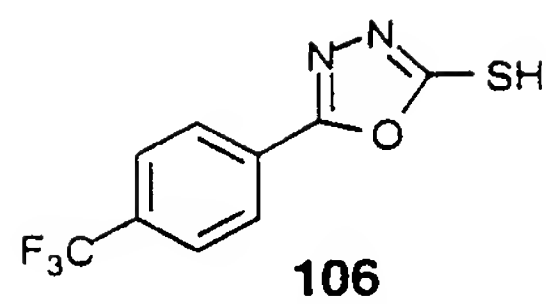
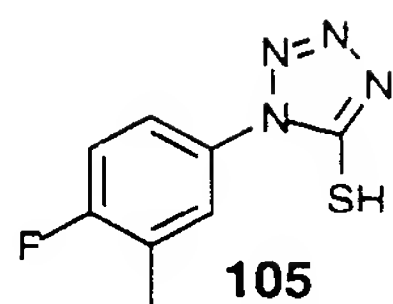
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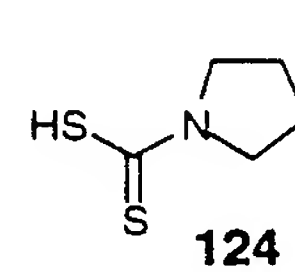
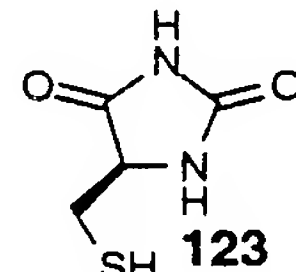
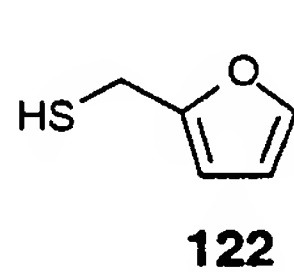
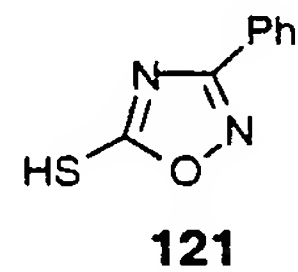
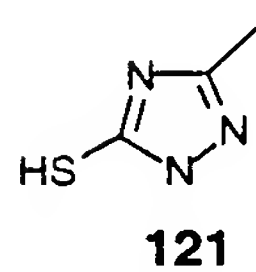
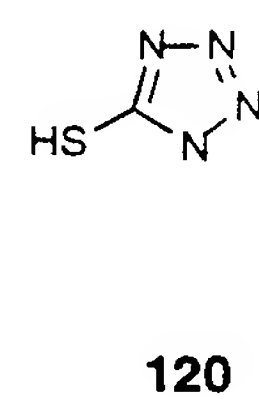
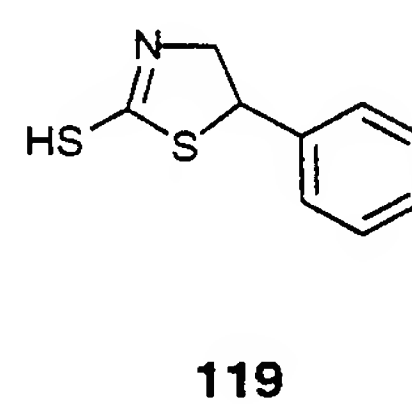
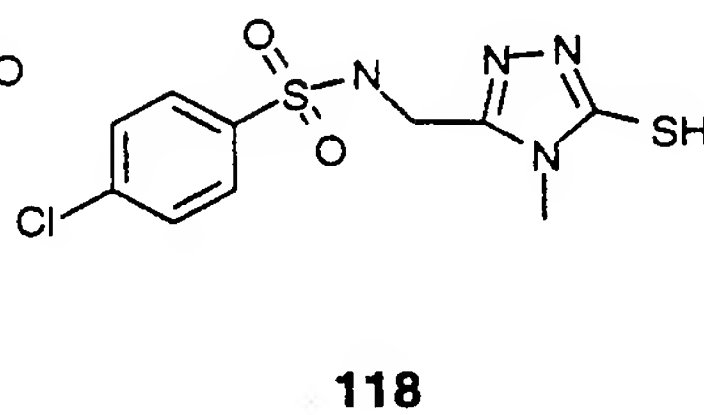
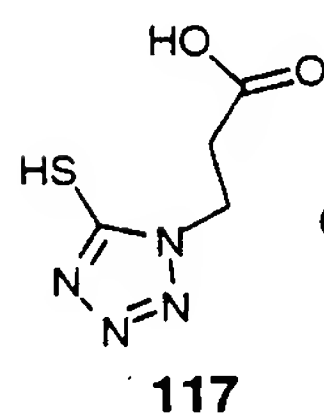
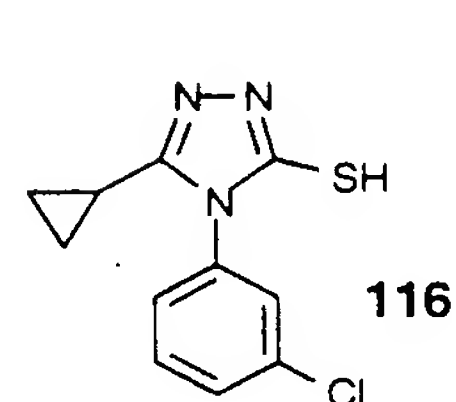
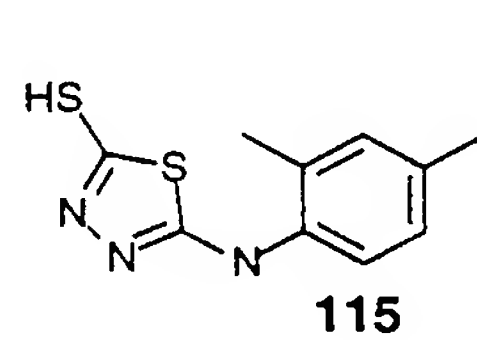
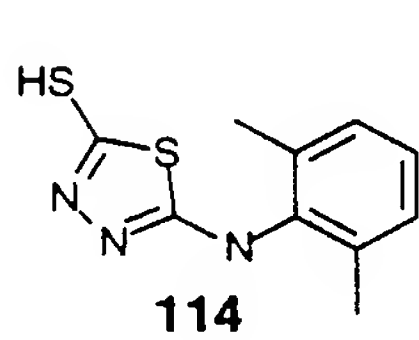
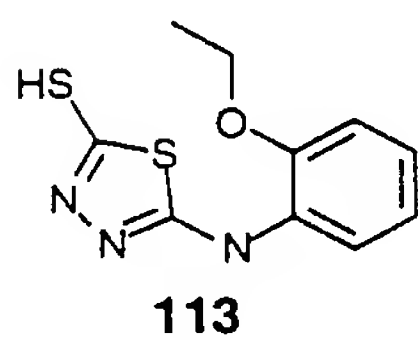
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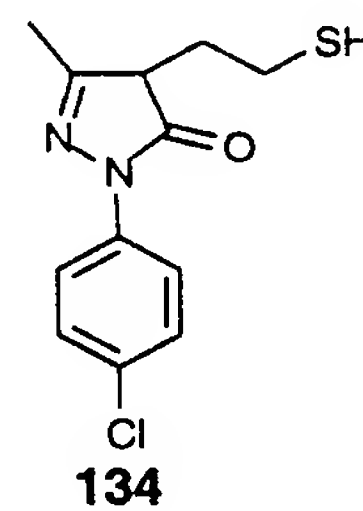
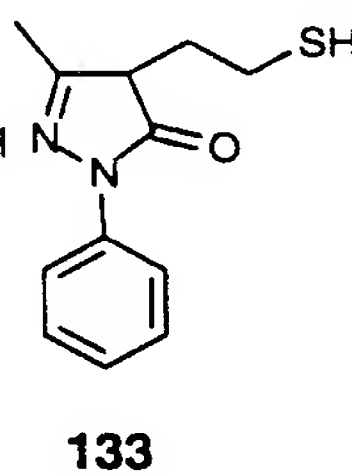
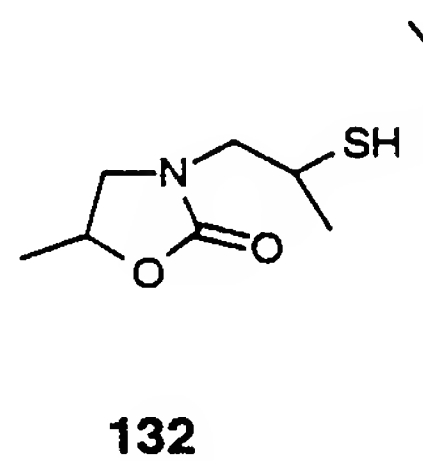
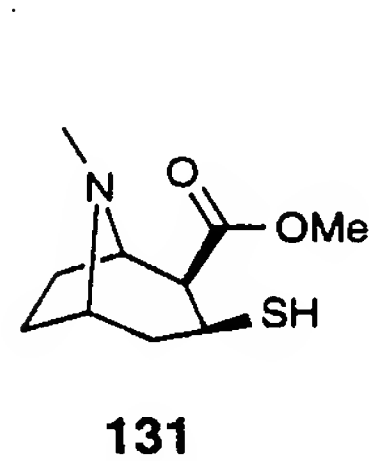
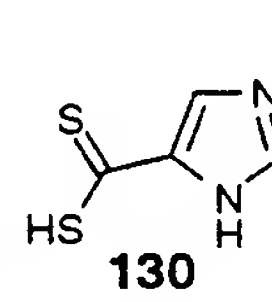
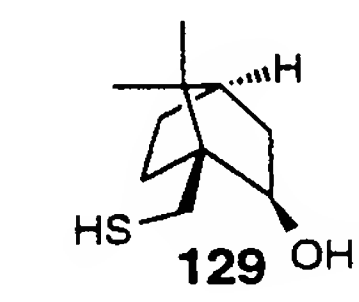
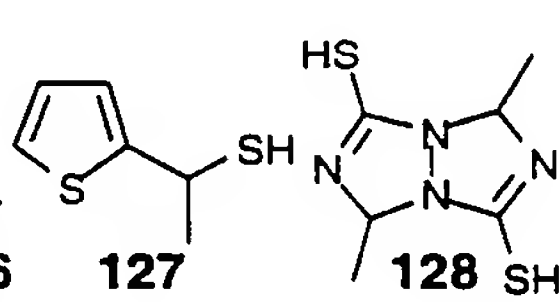
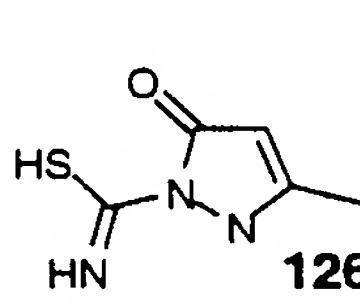
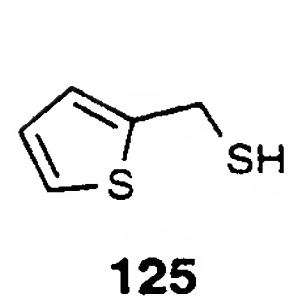




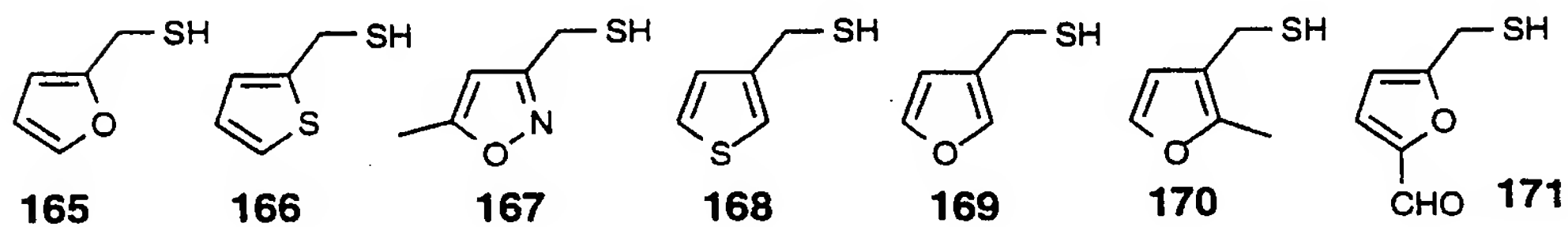
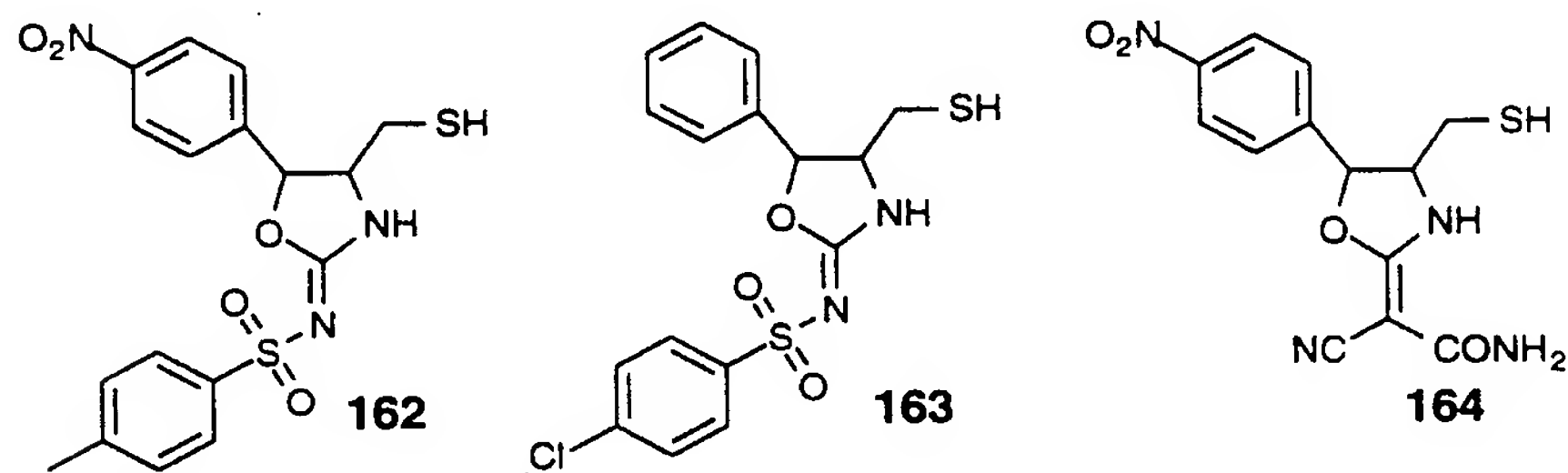
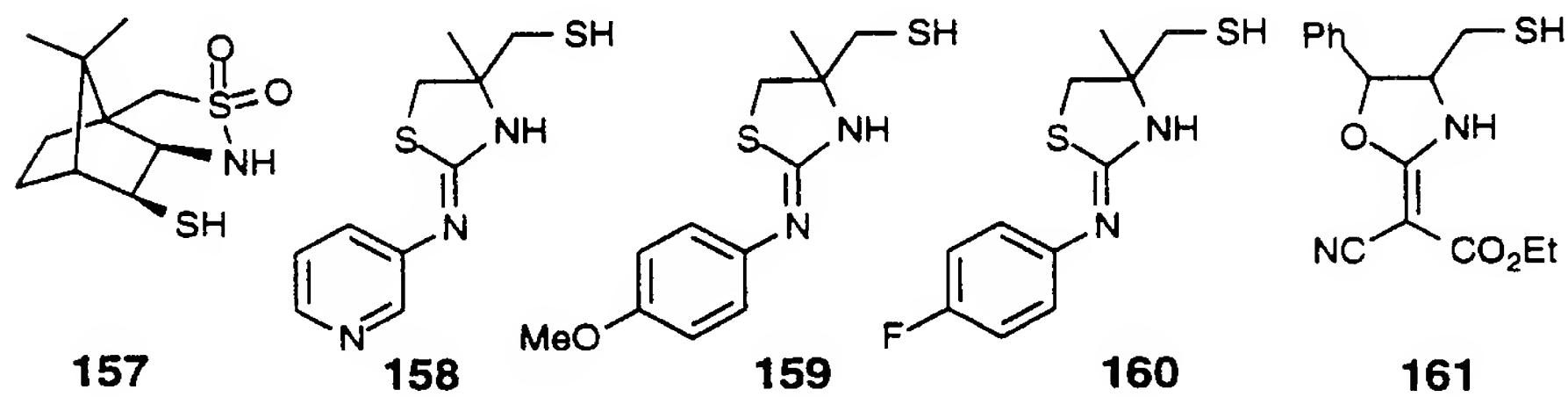
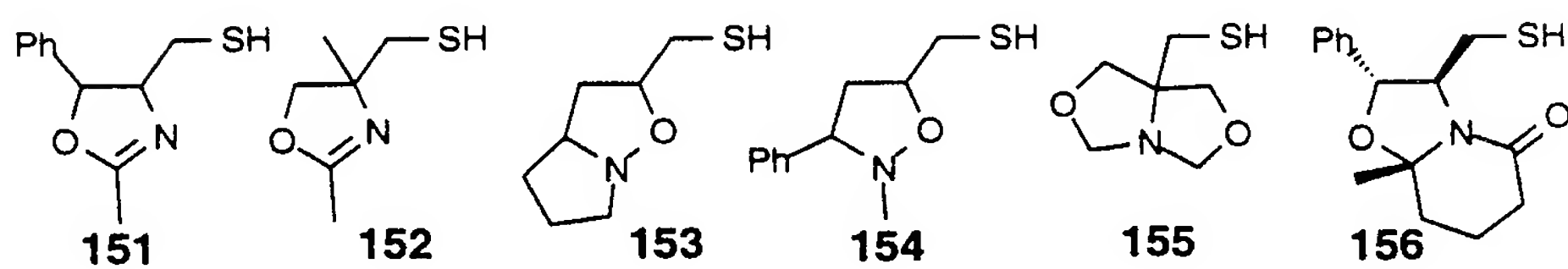
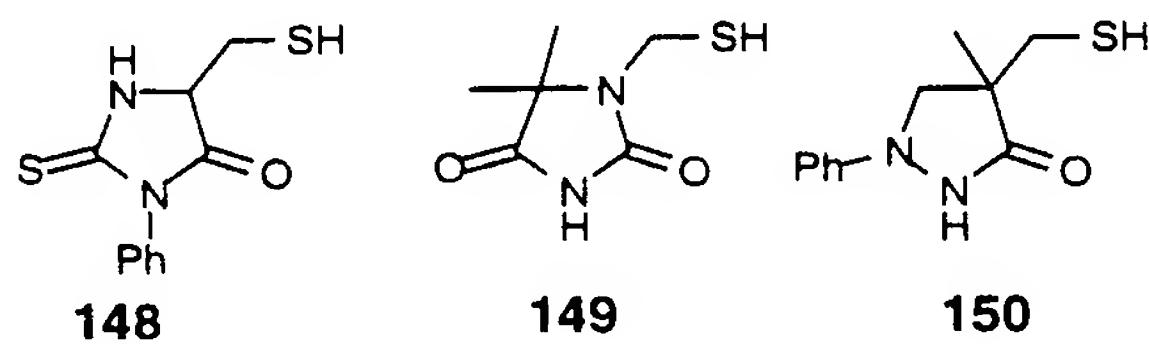
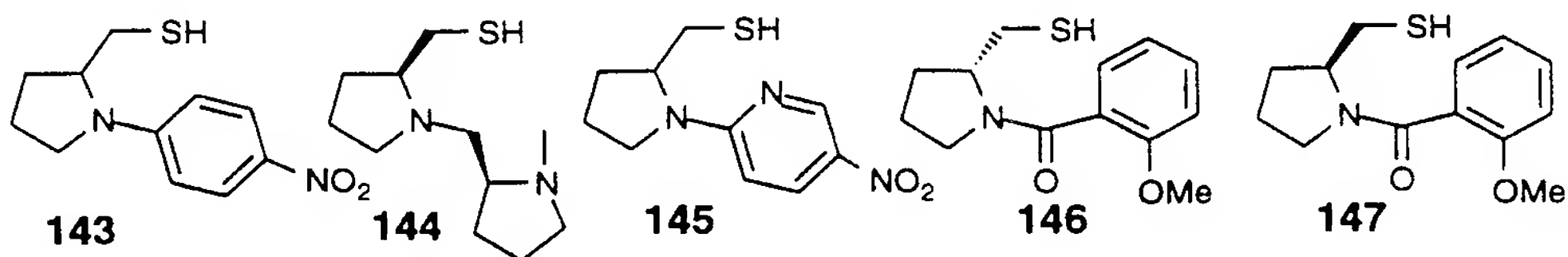
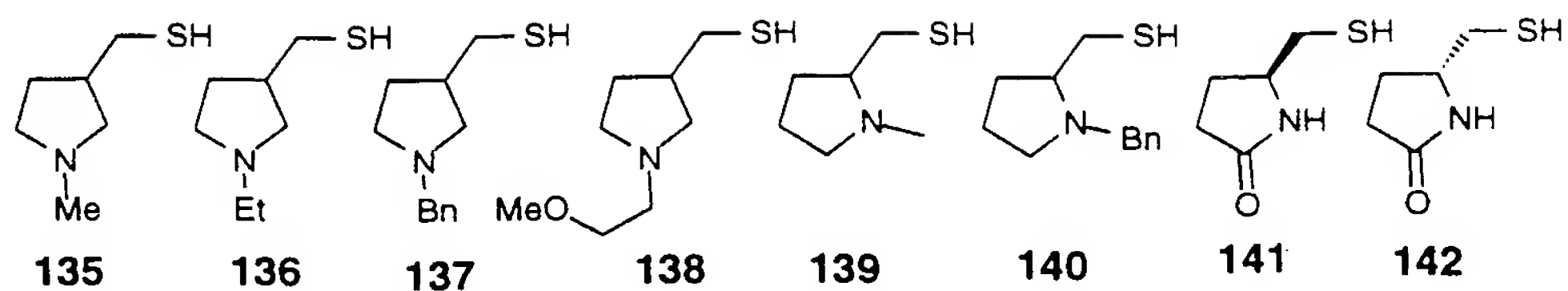
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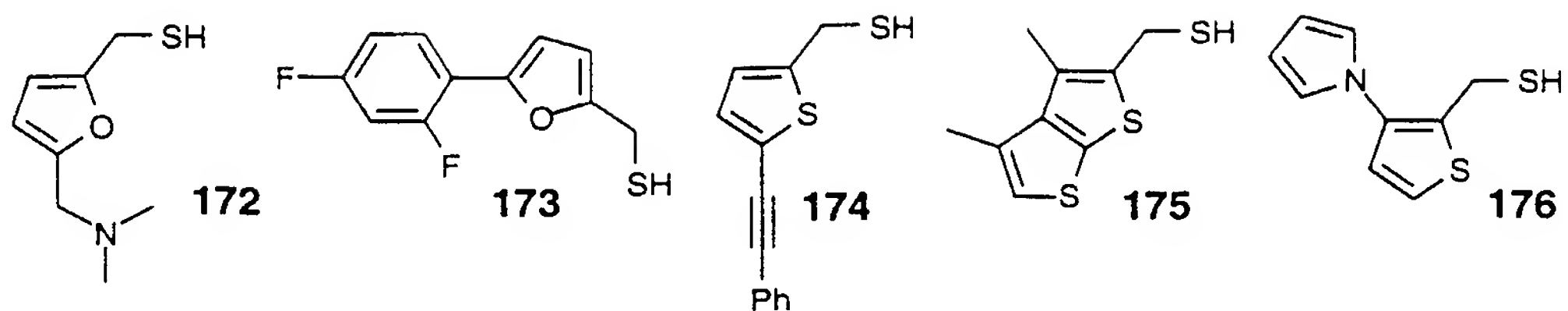


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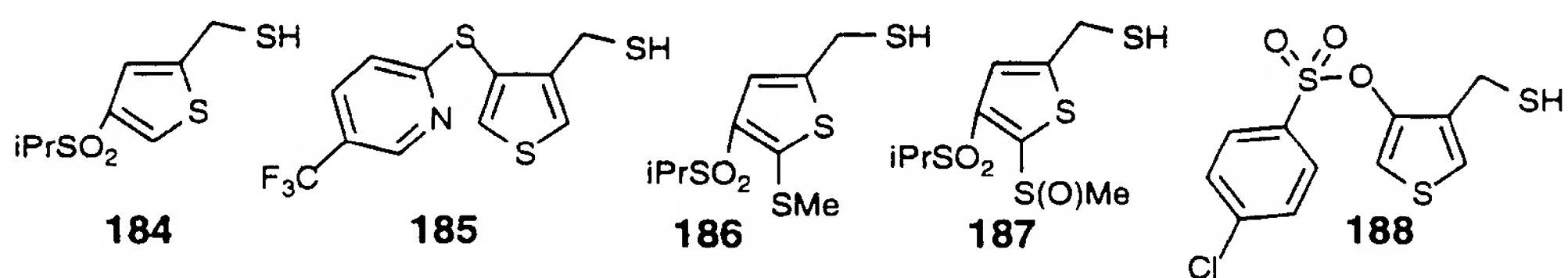
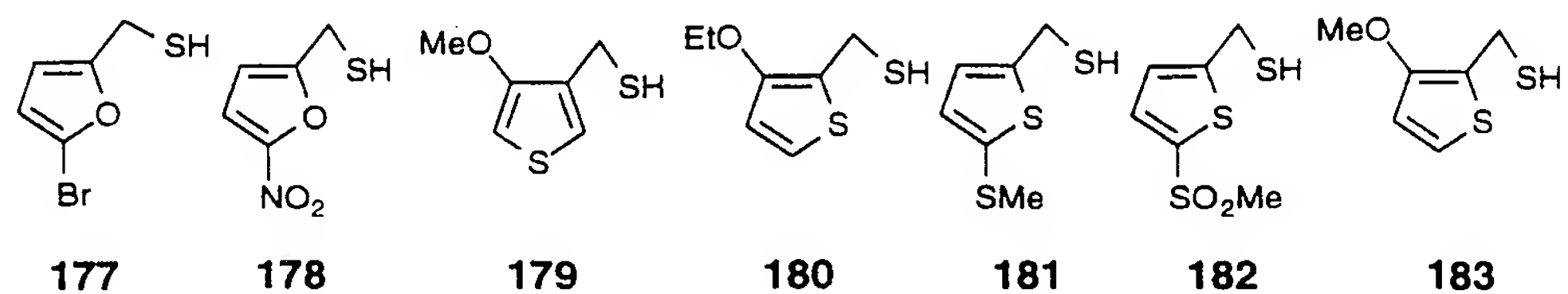


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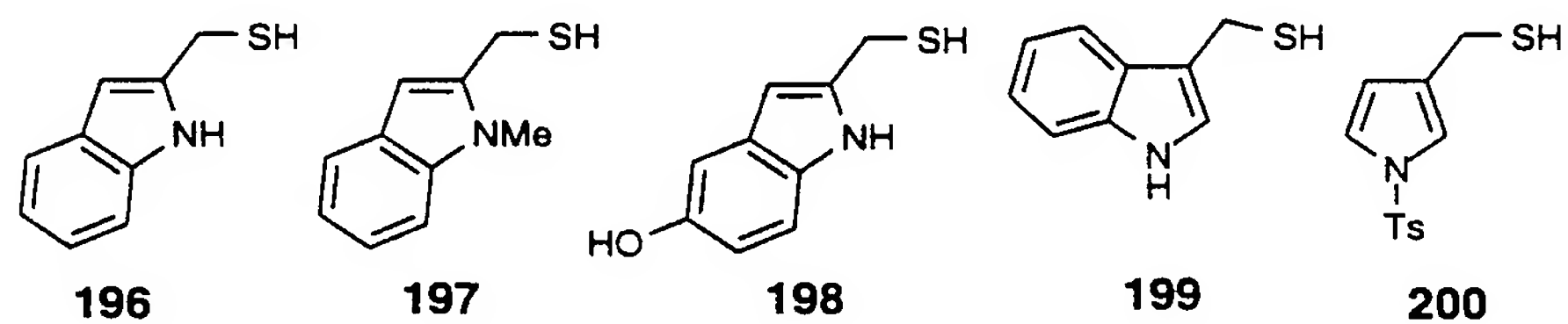
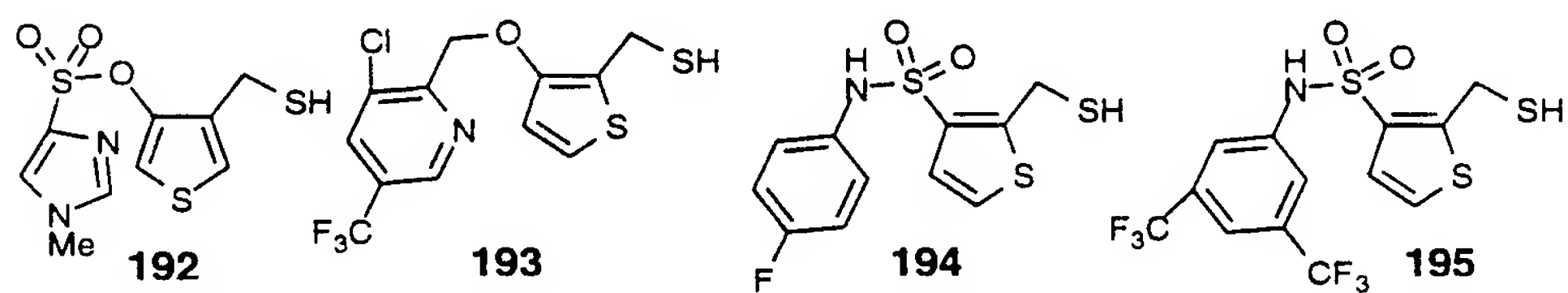
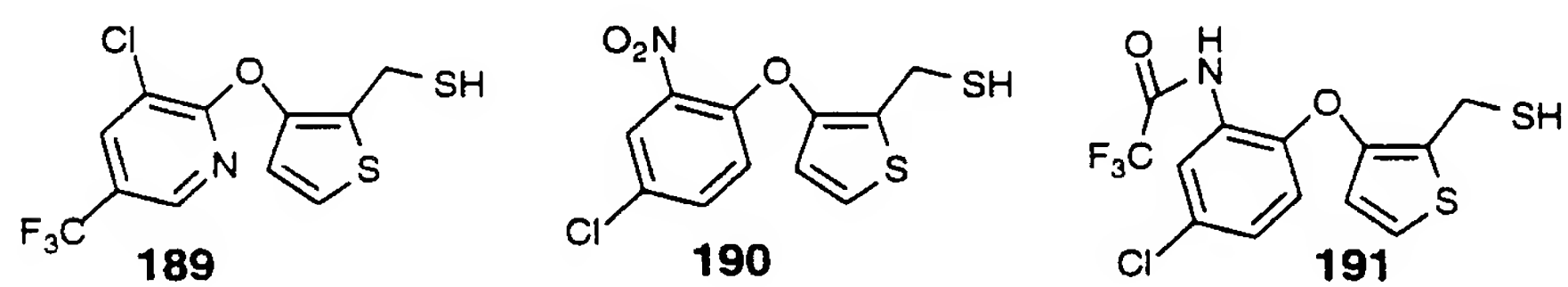




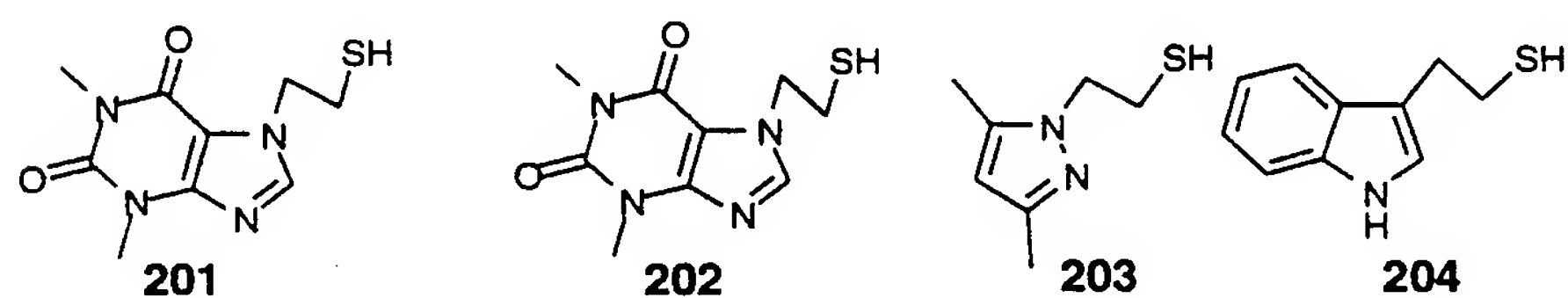
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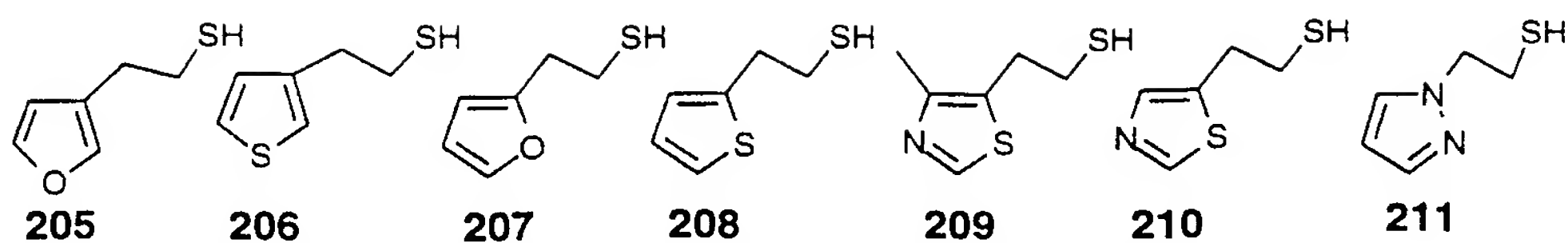


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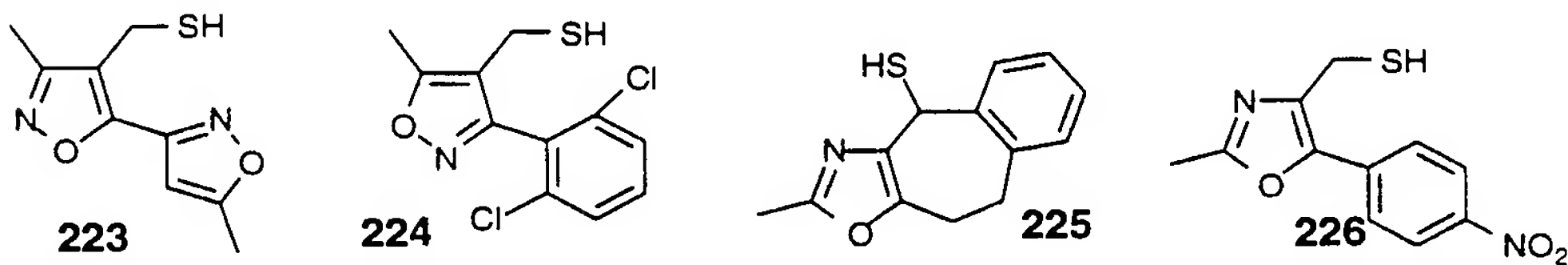
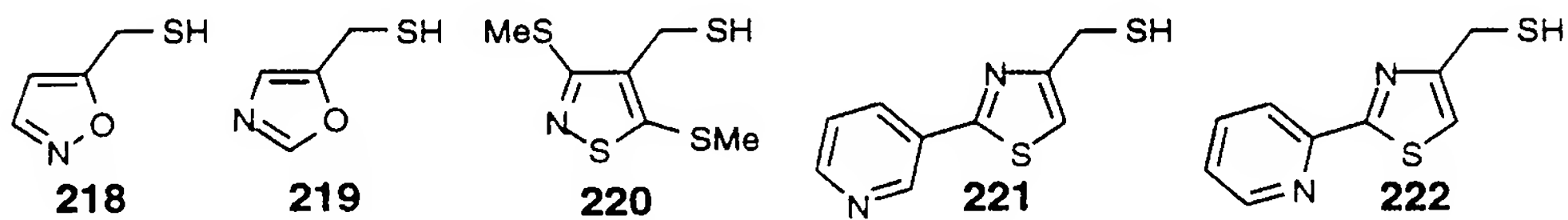
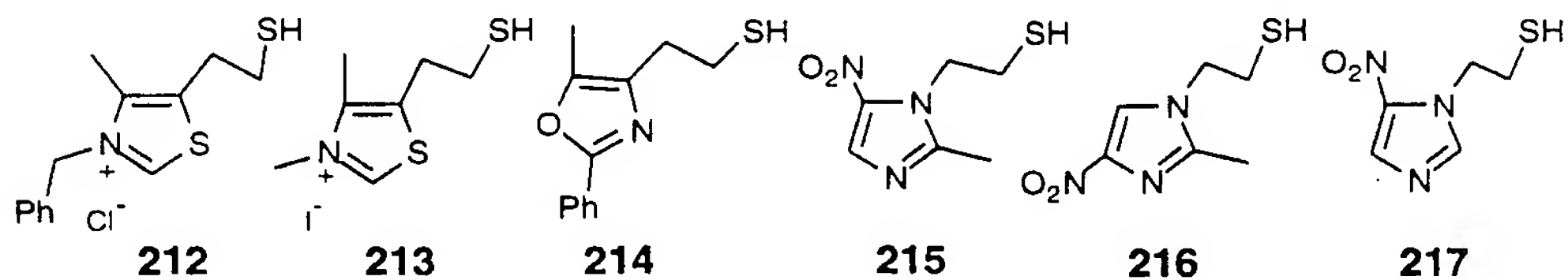


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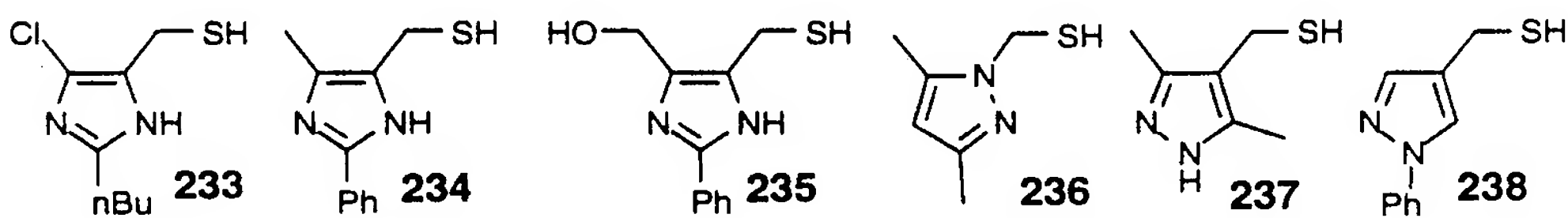
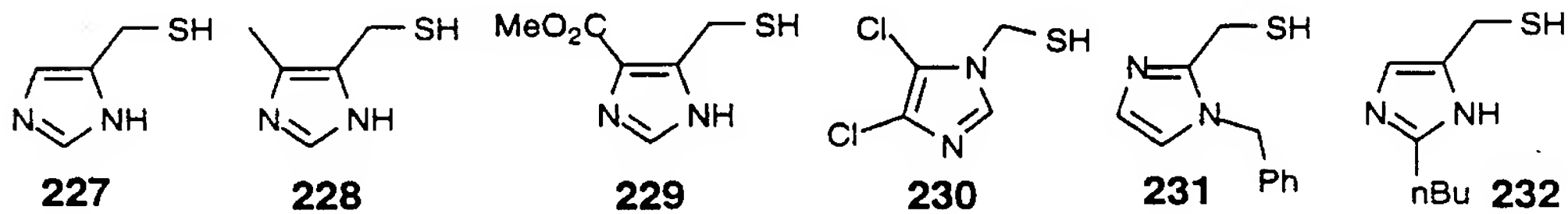




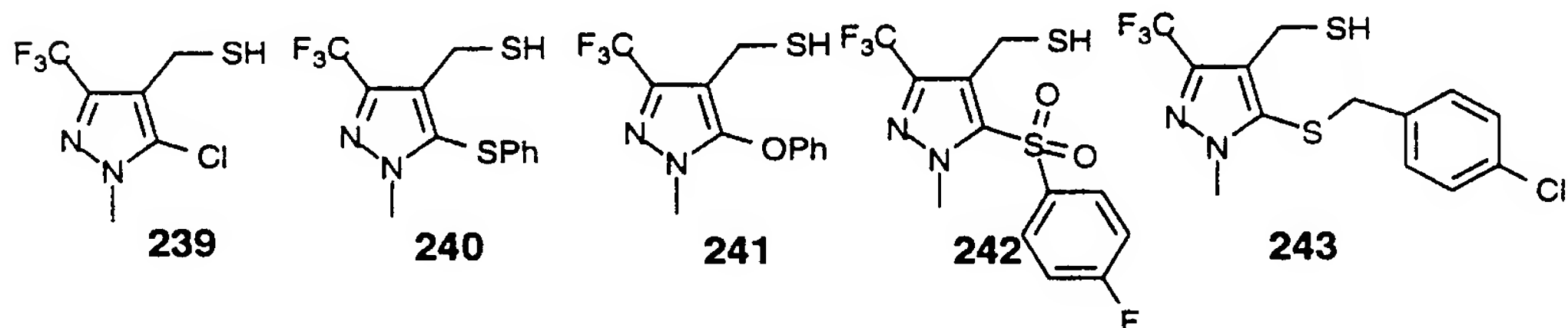
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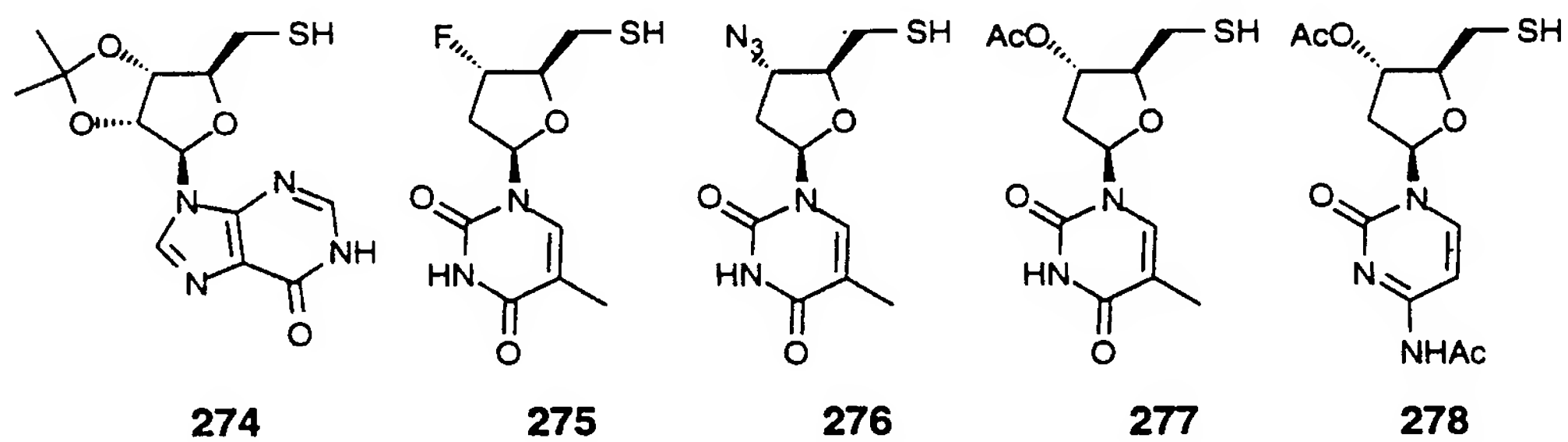
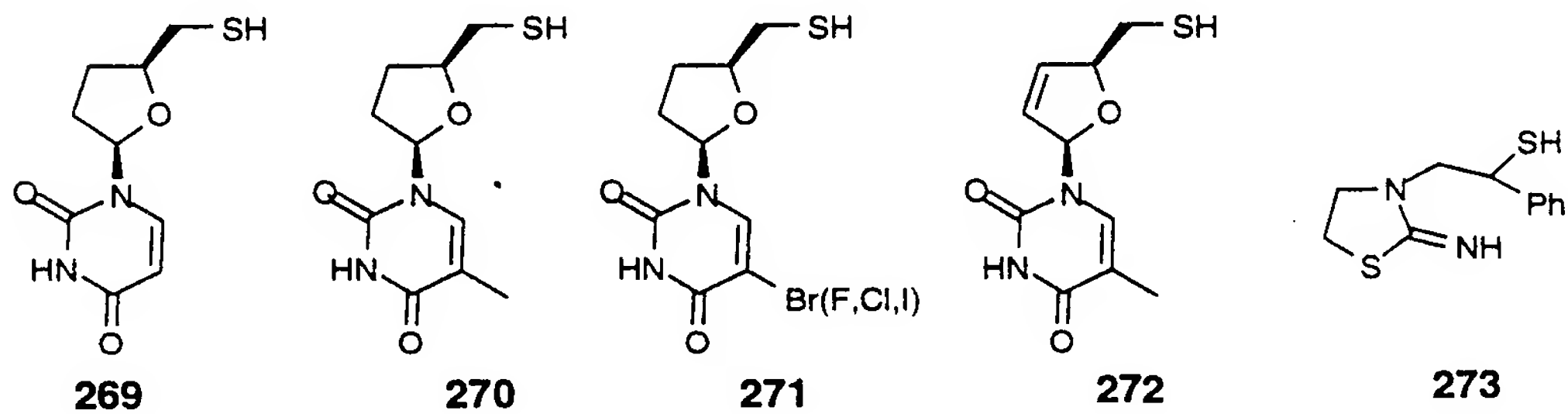
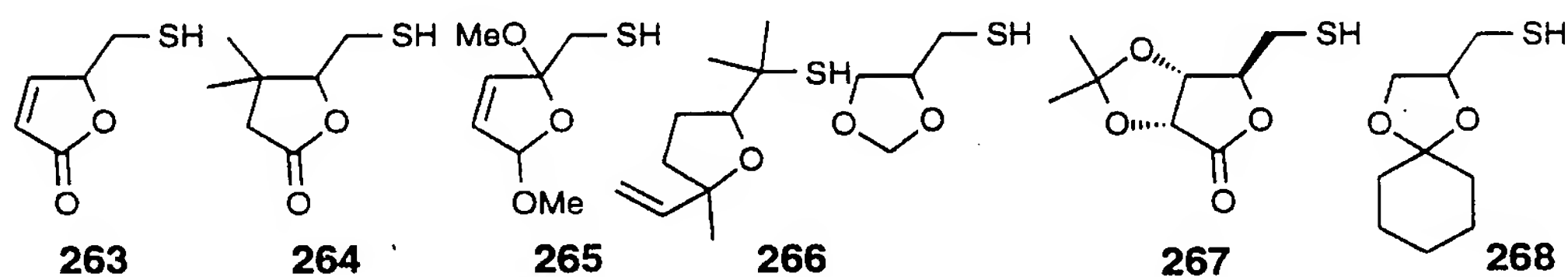
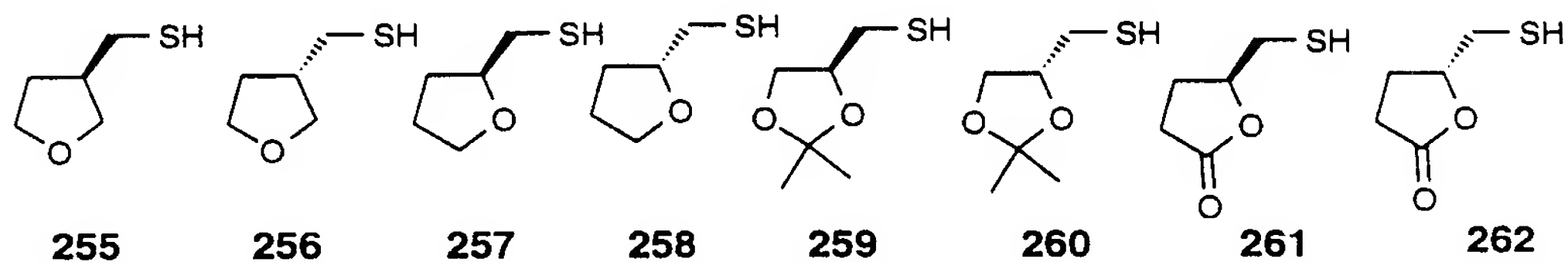
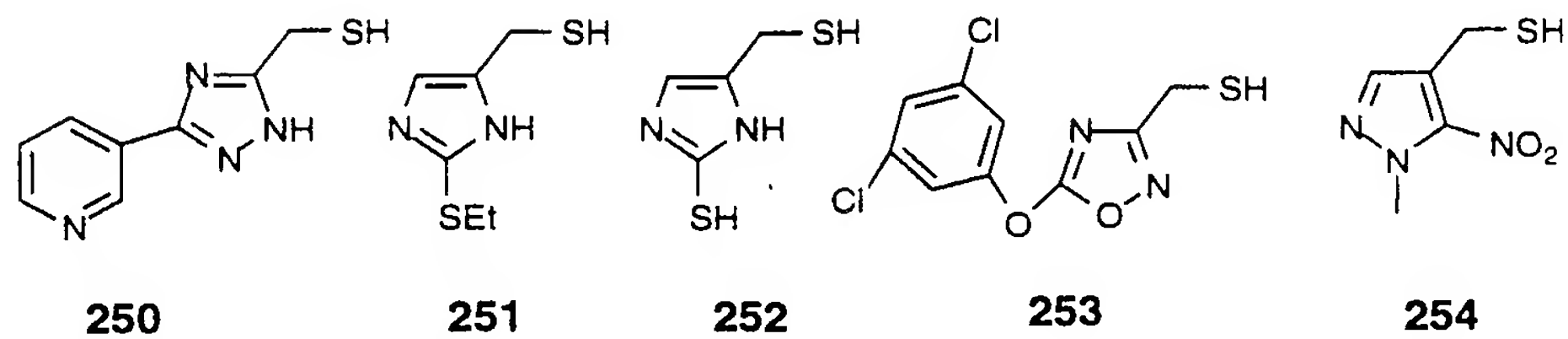
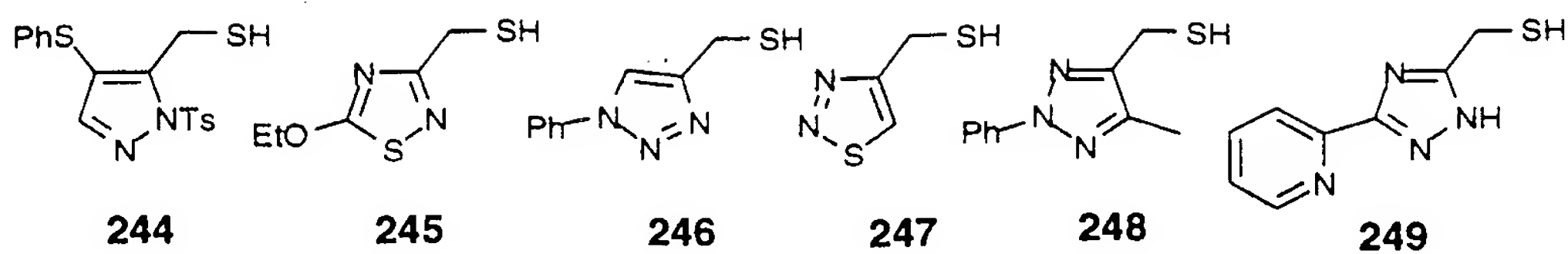


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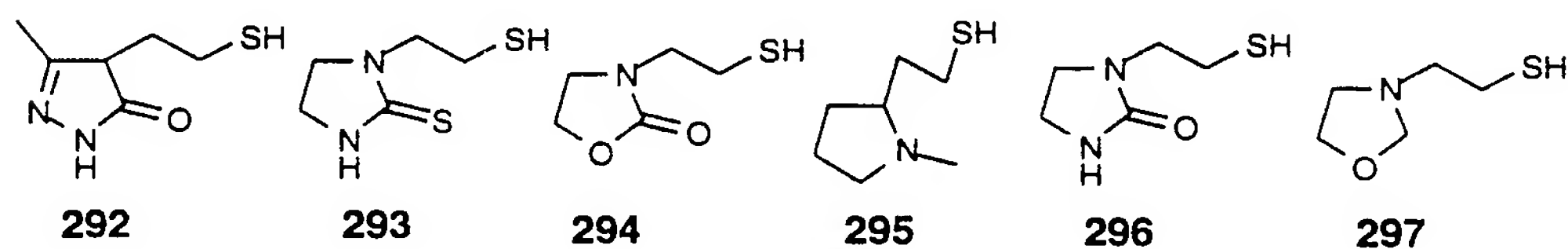
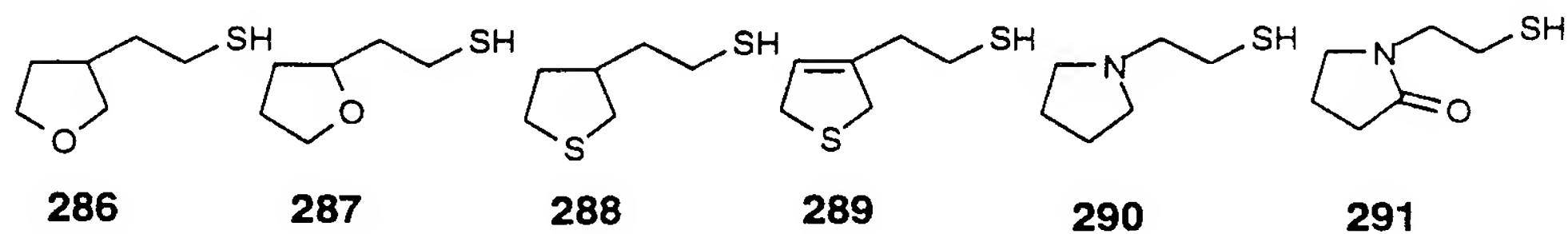
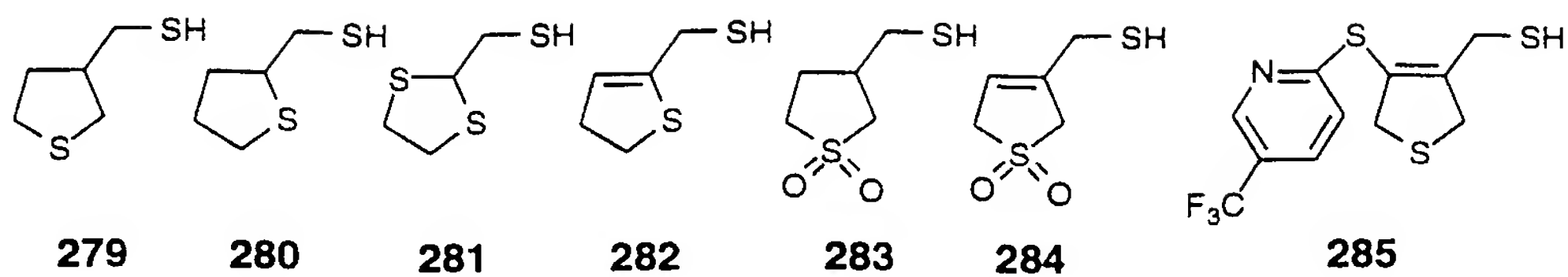


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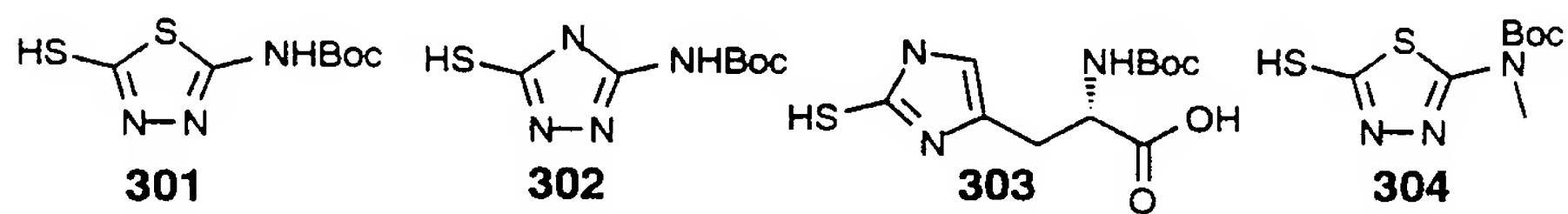
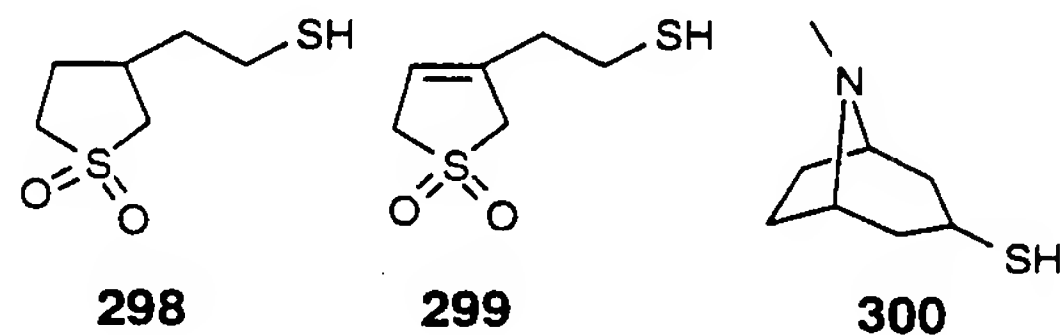




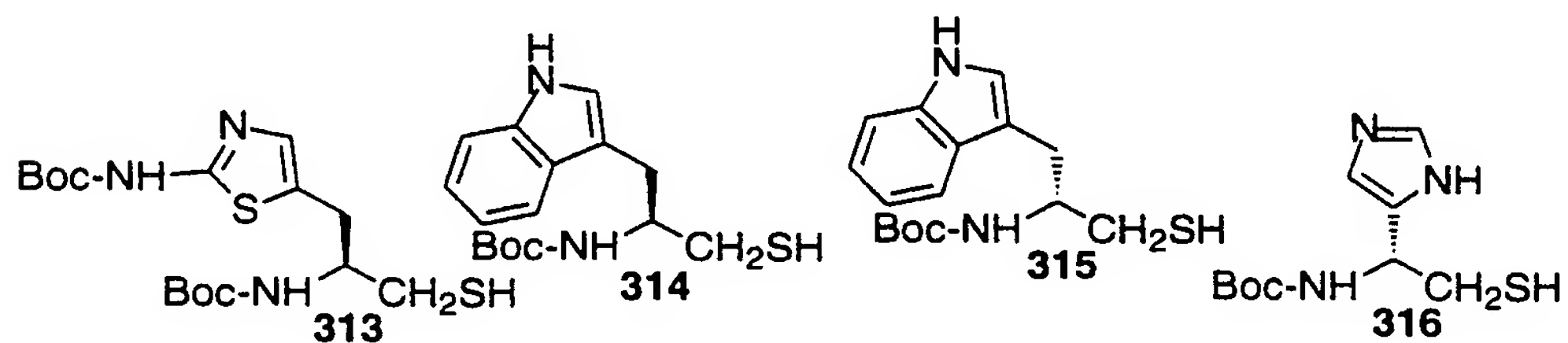
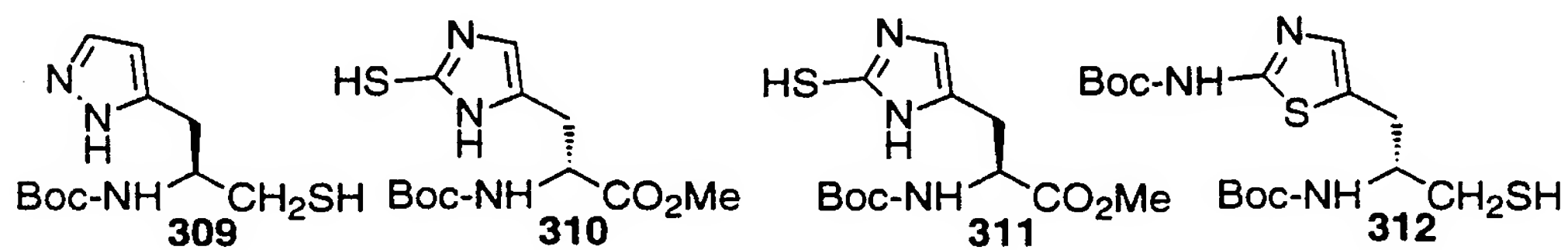
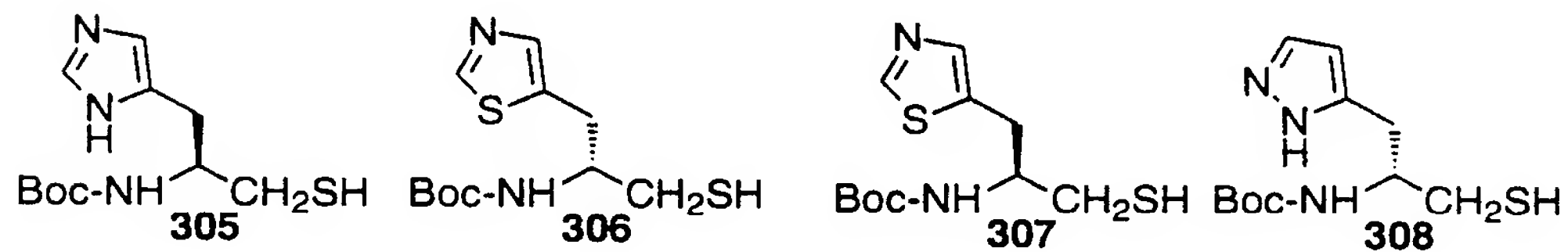
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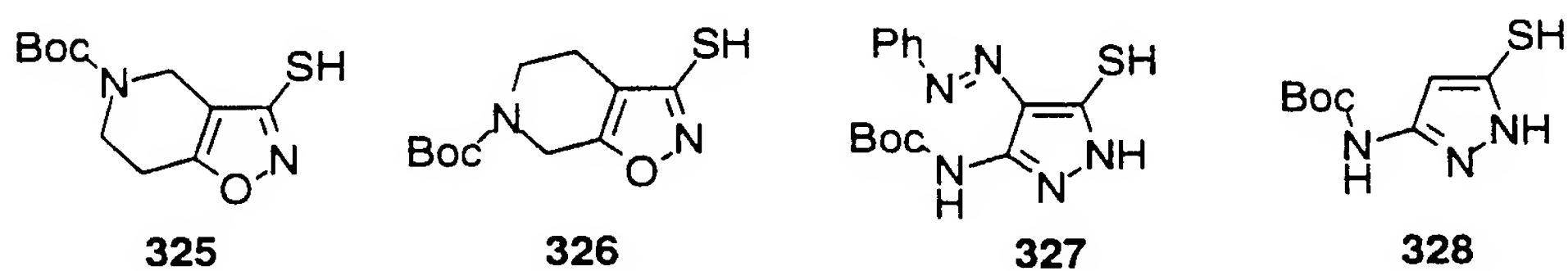
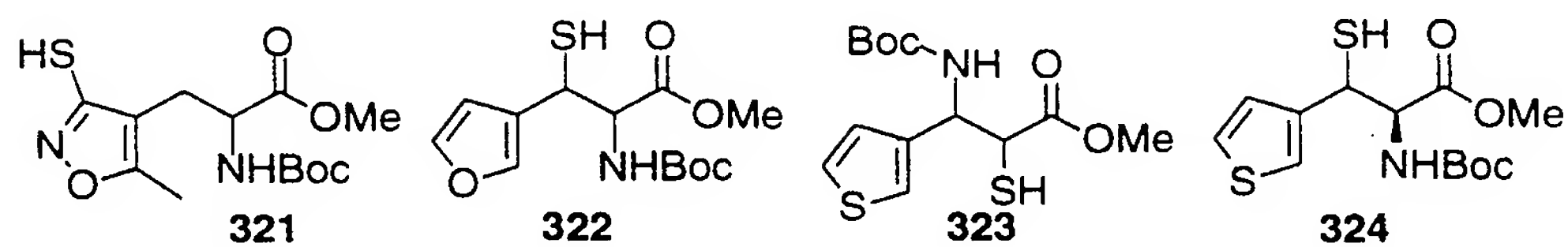
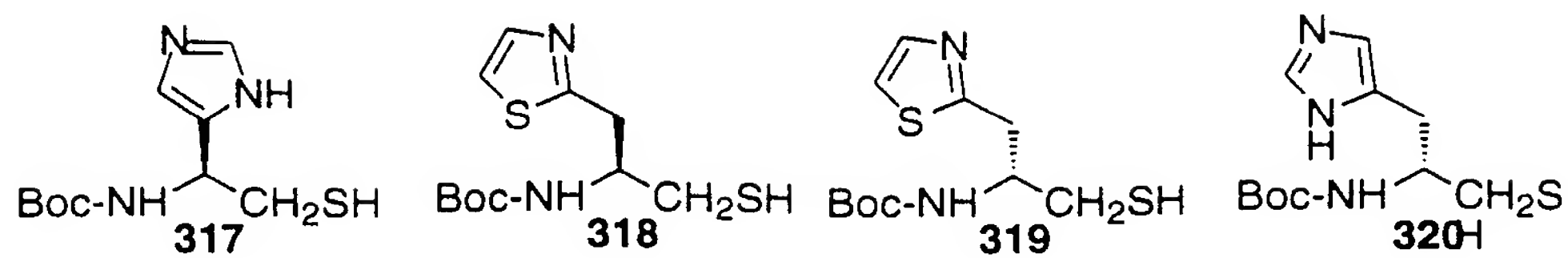


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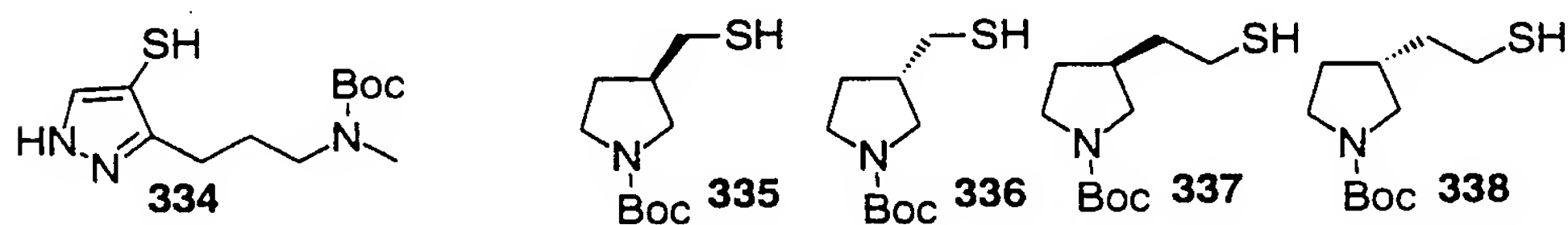
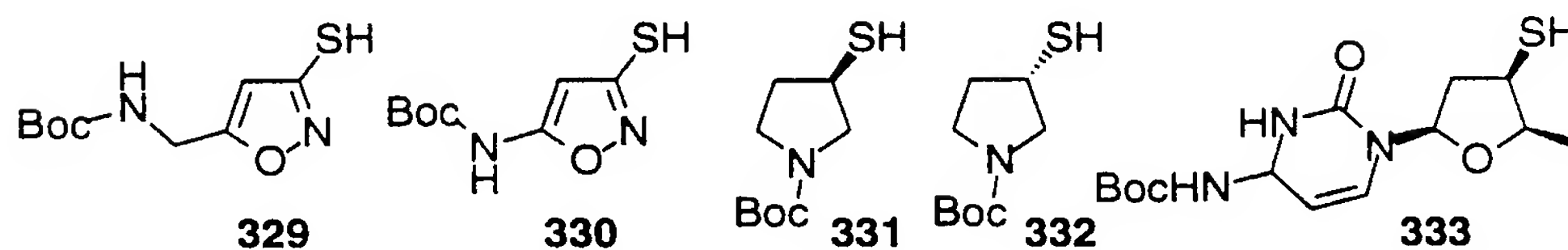




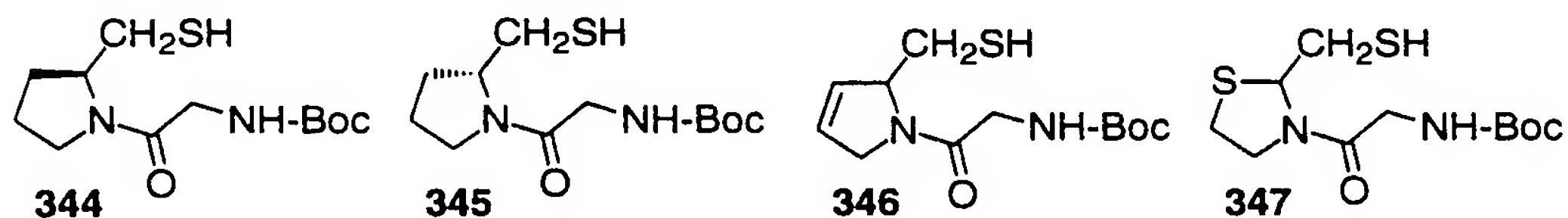
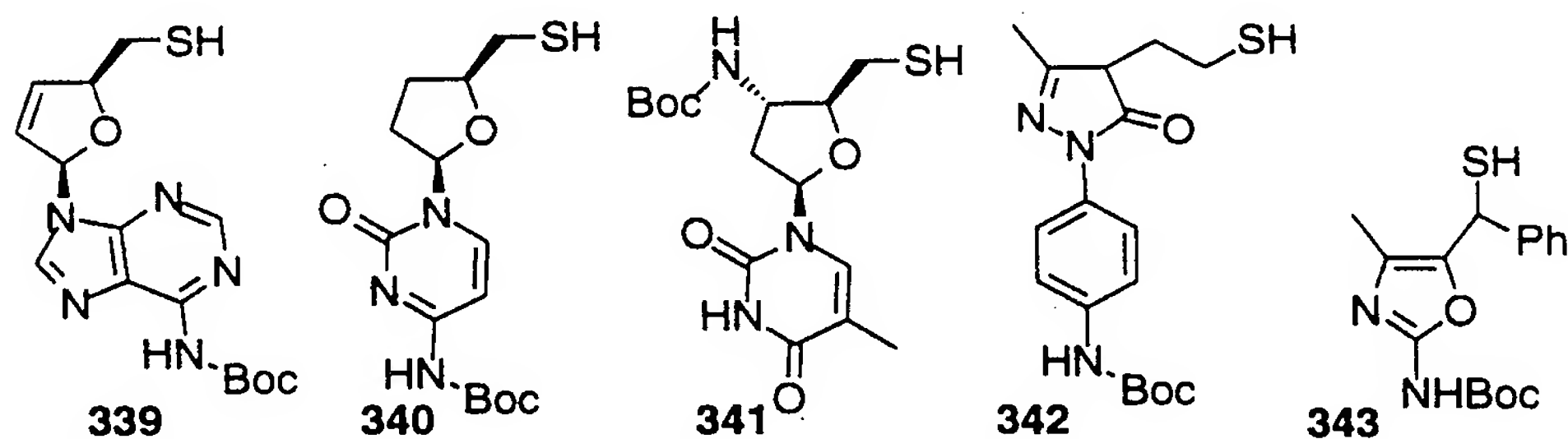
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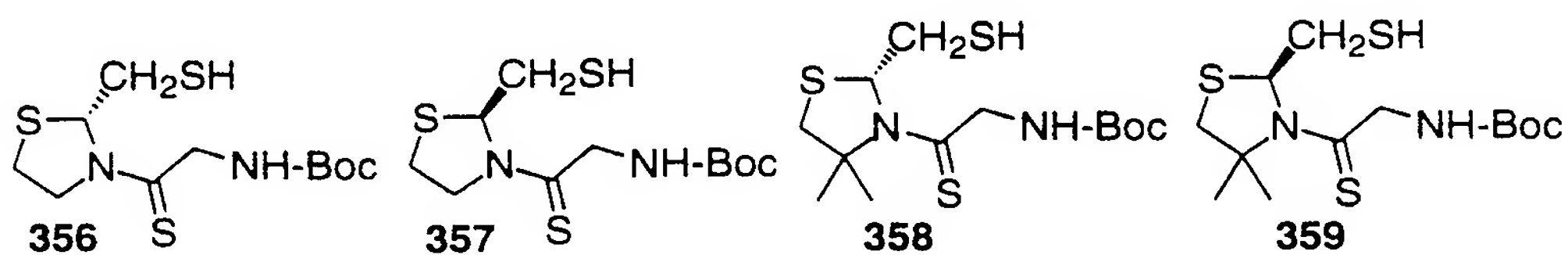
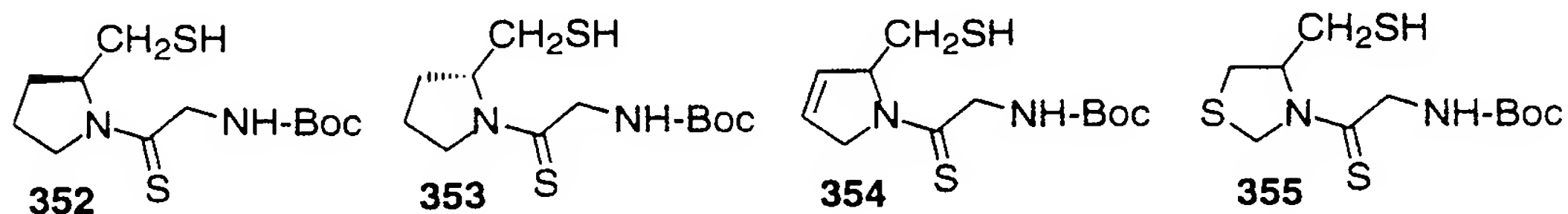
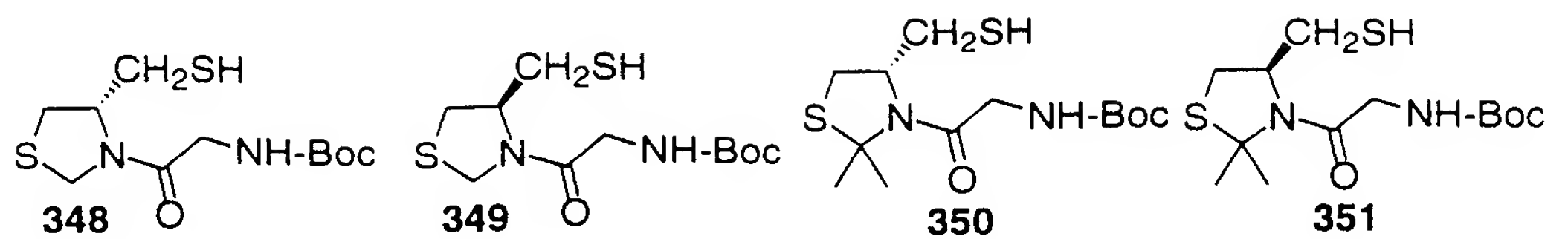
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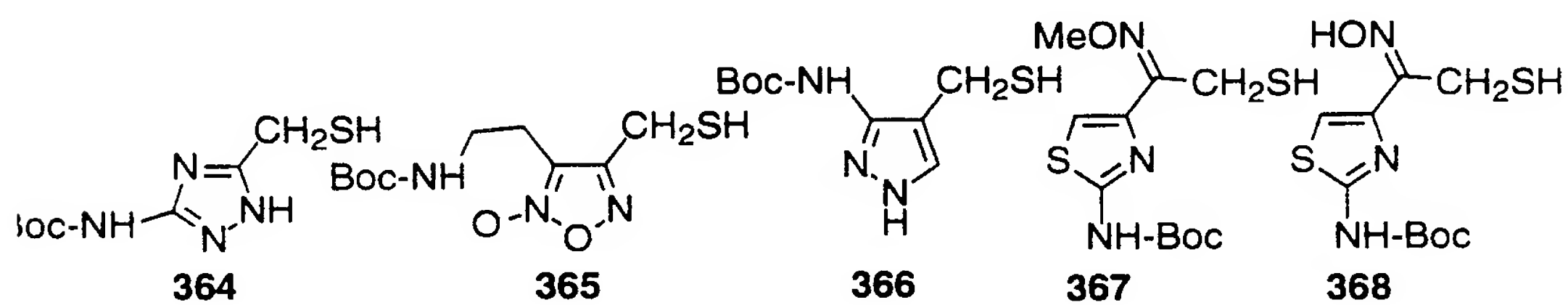
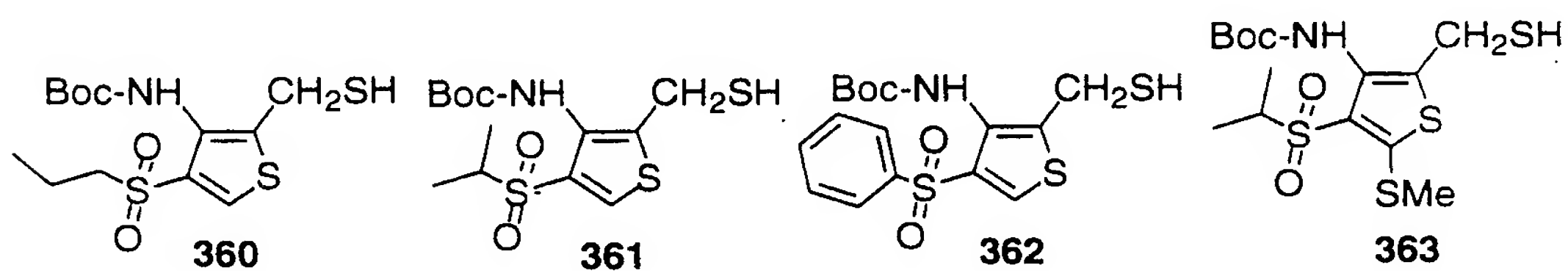
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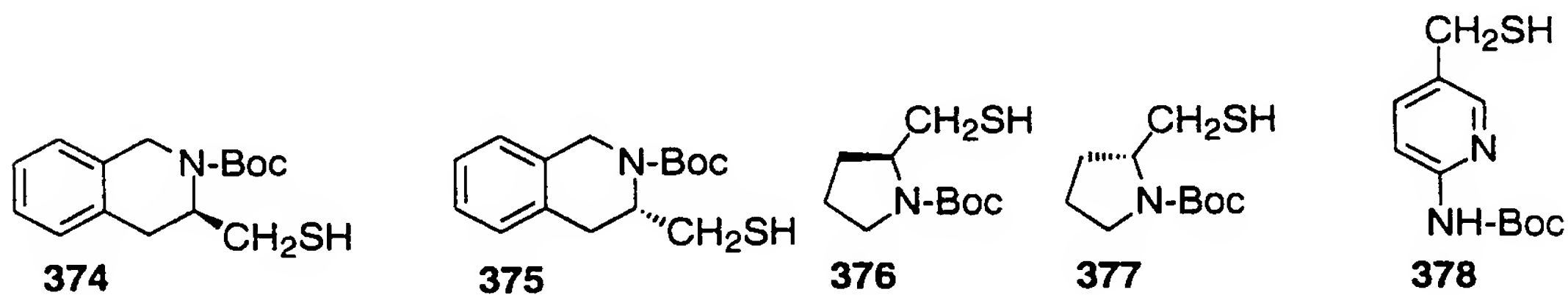
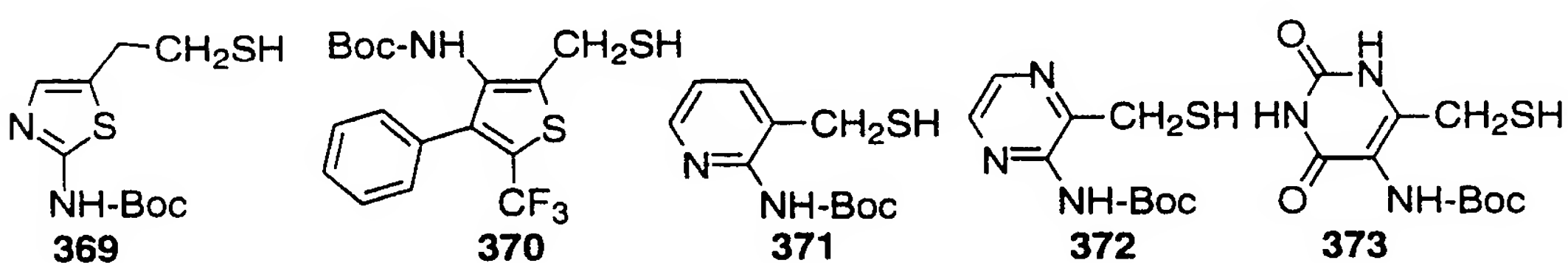
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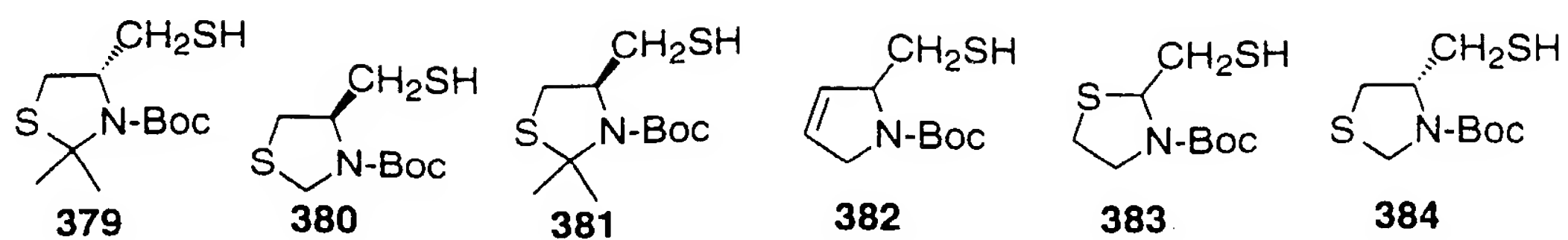


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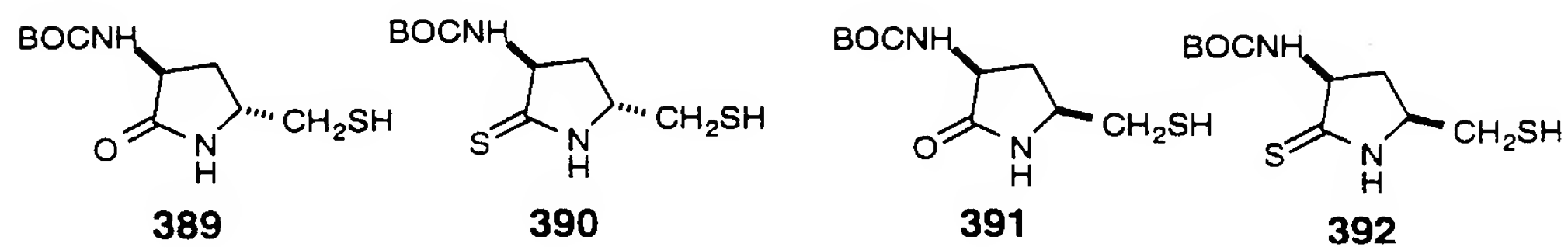
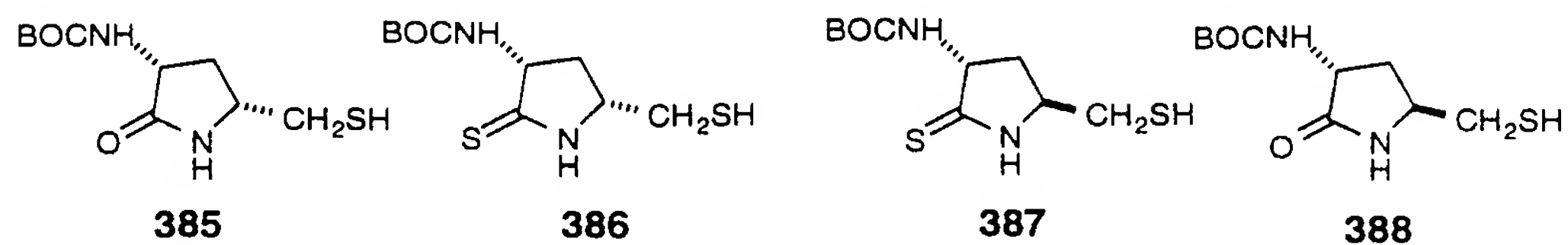


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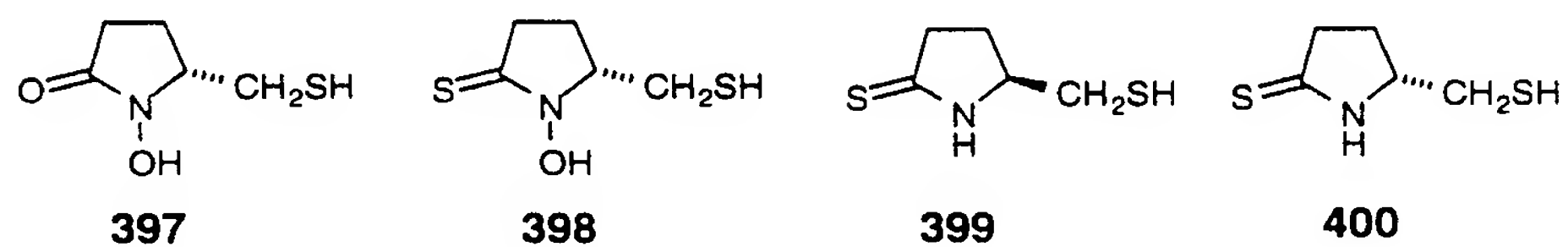
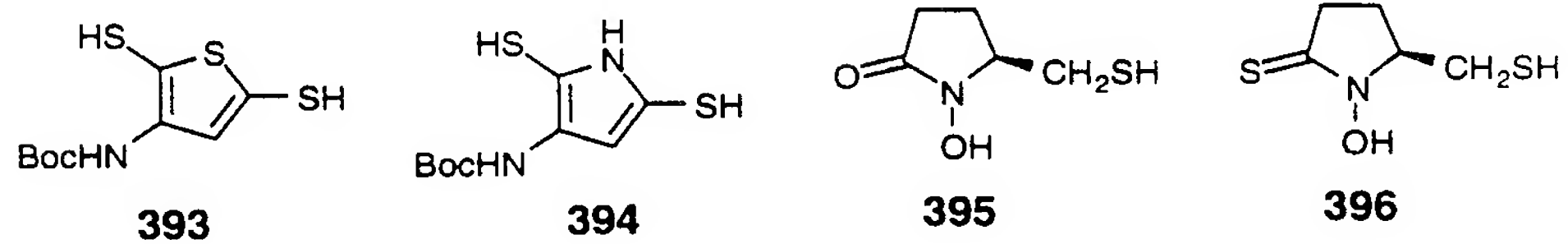




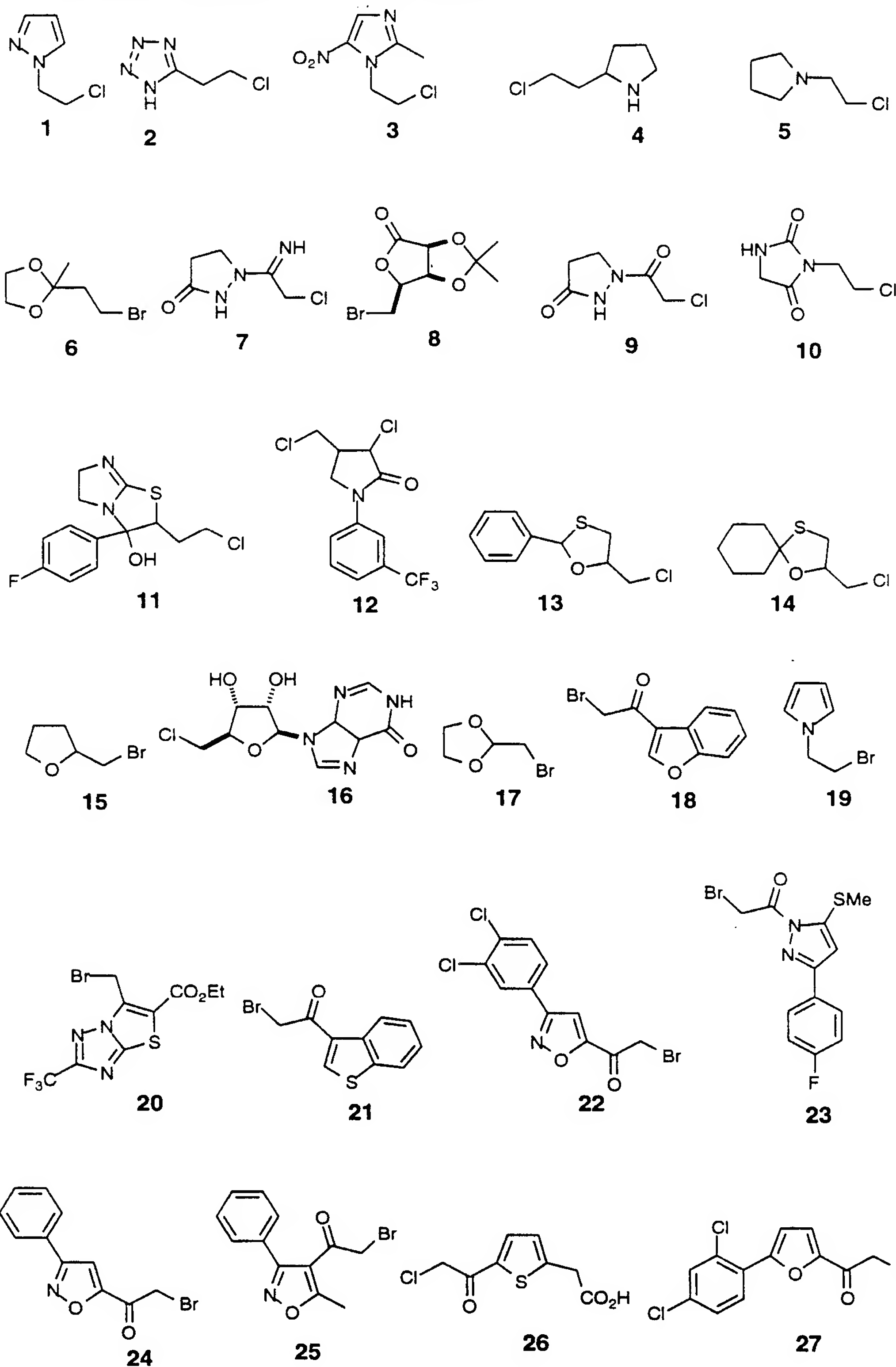
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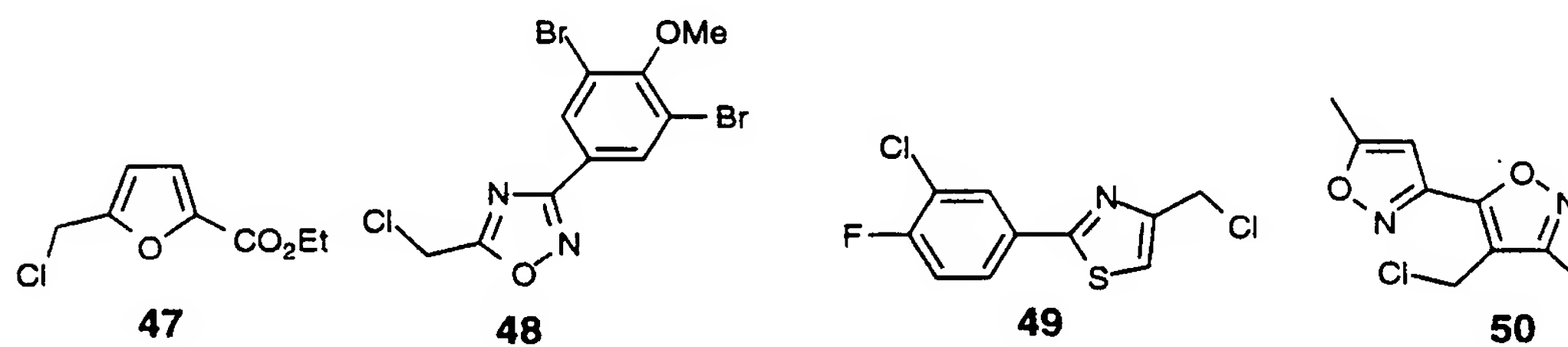
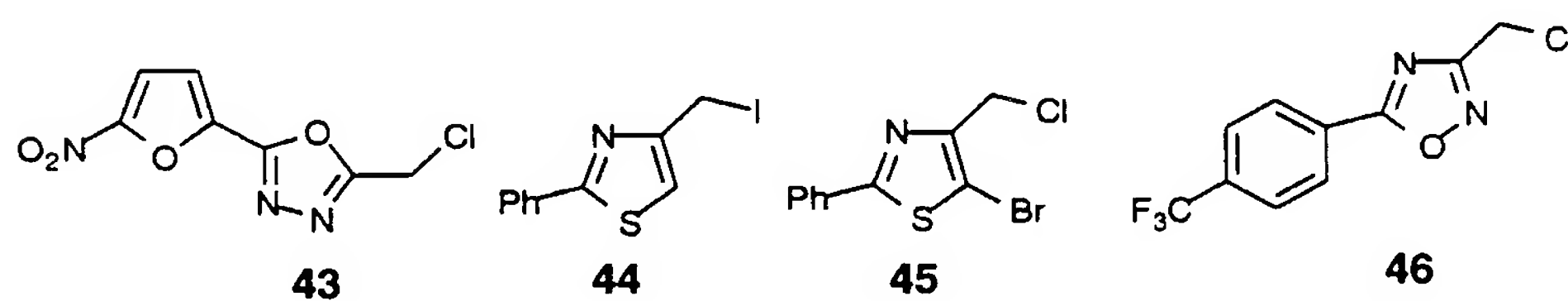
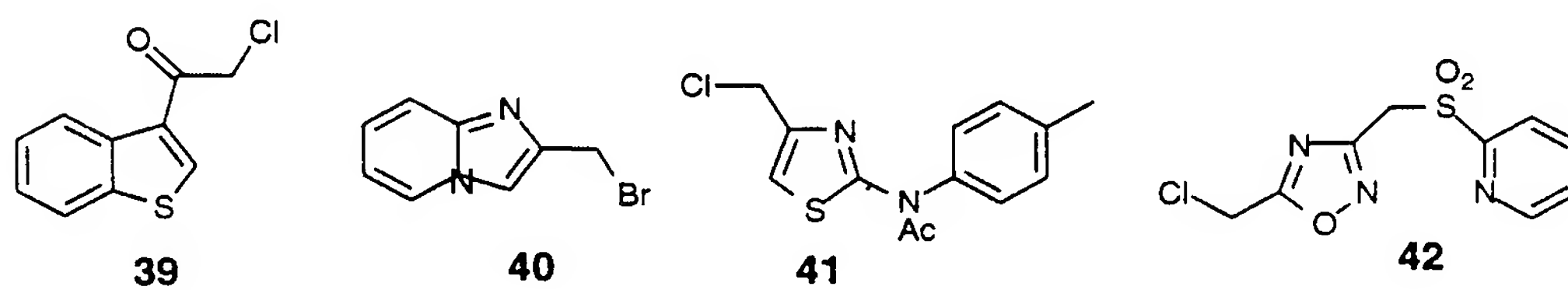
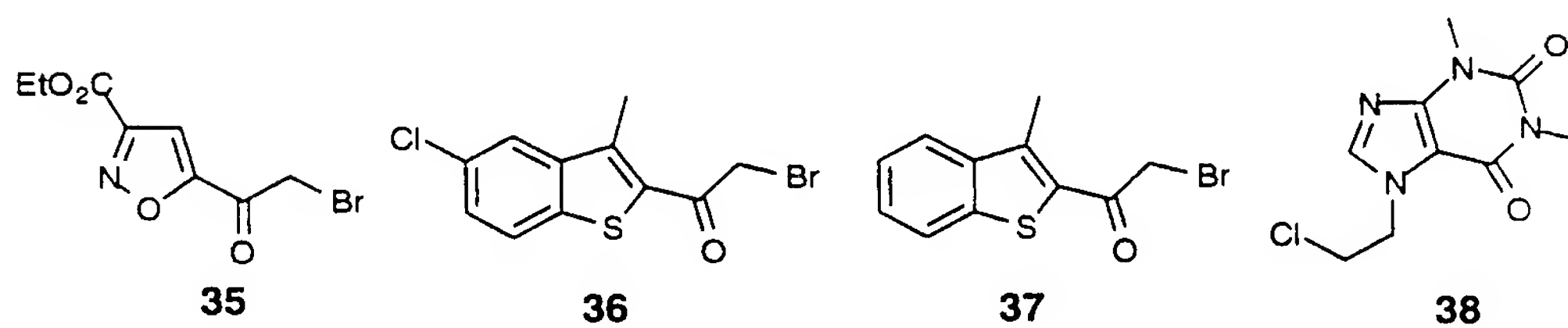
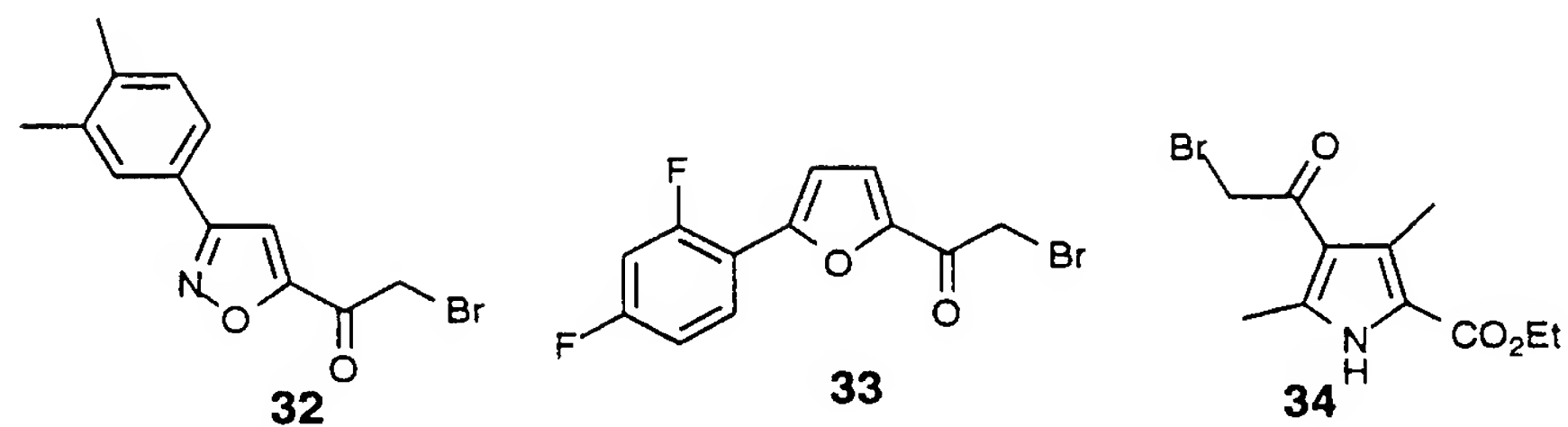
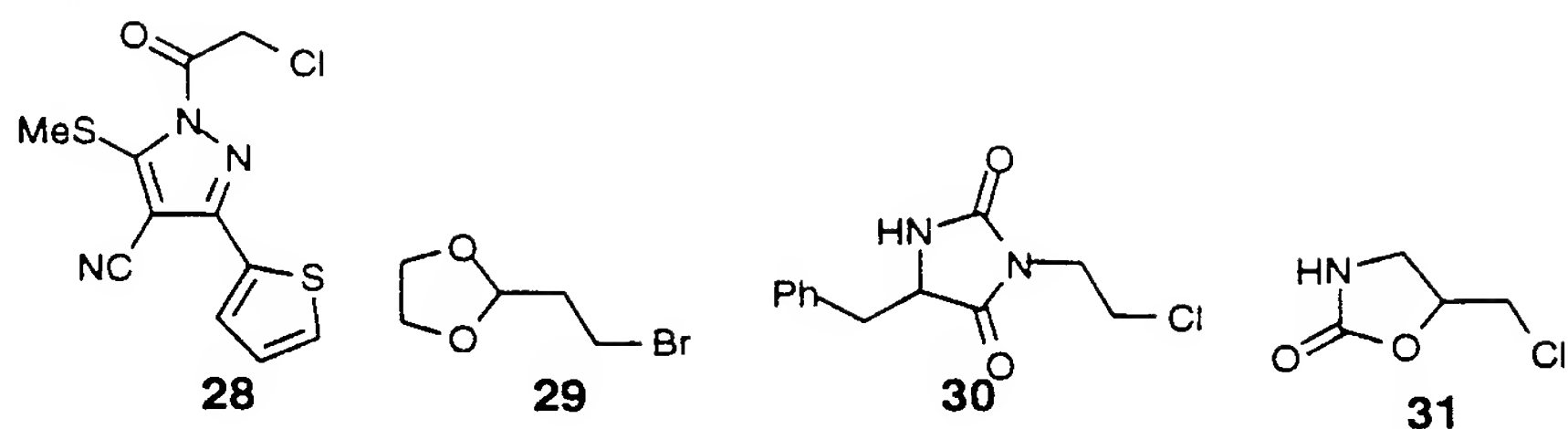


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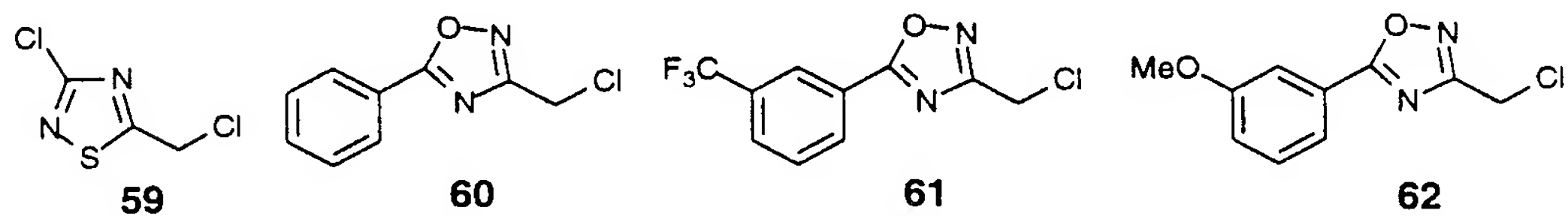
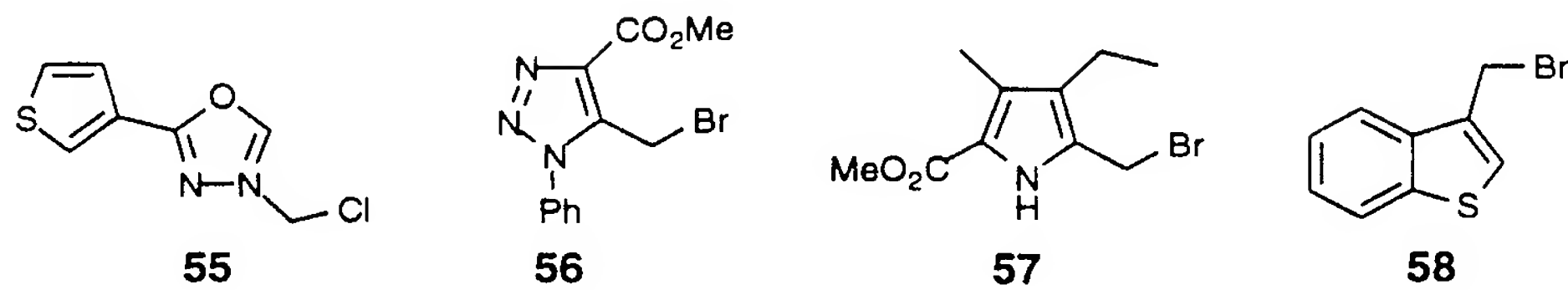
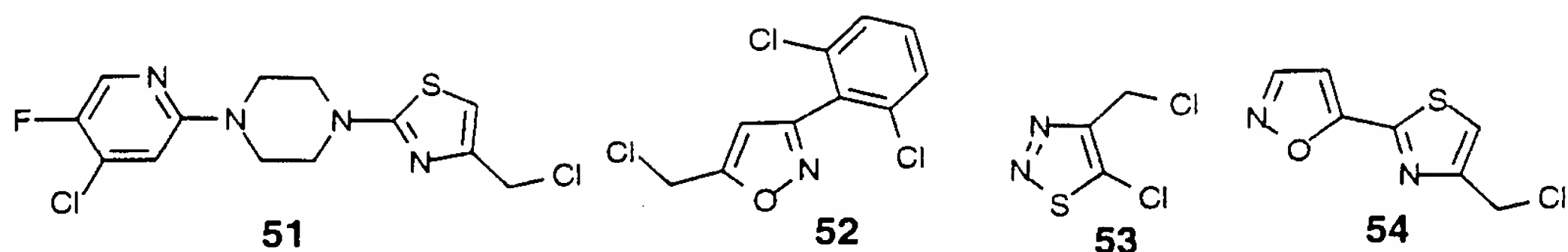


3380 Table 17. Halides of the type A-Cl, A-Br, and A-I

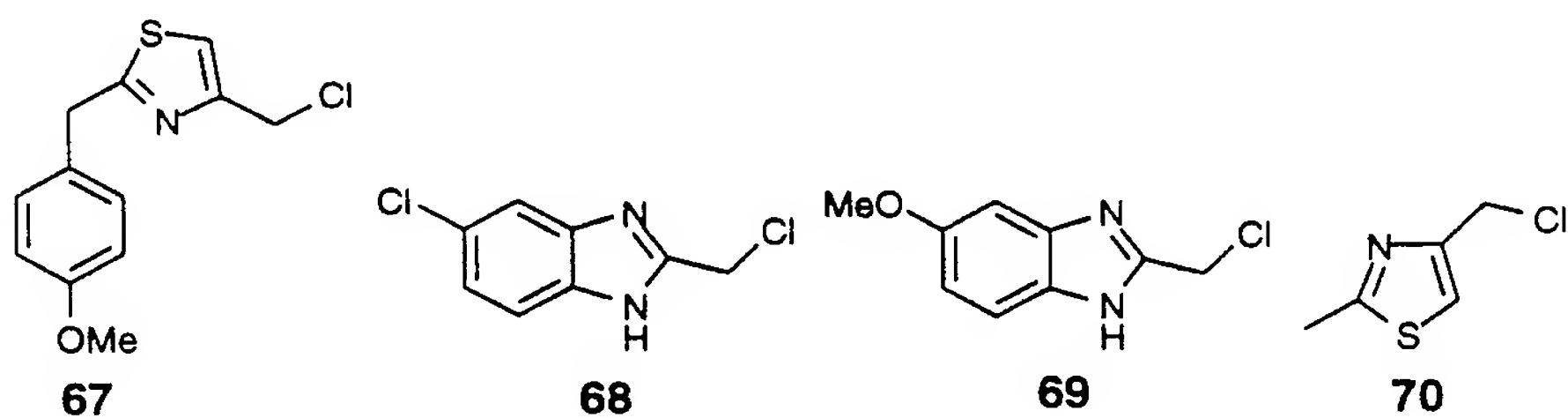
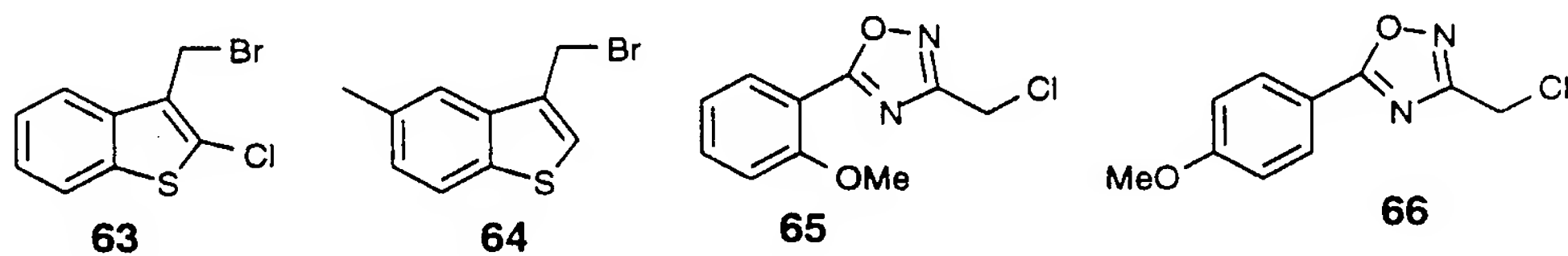




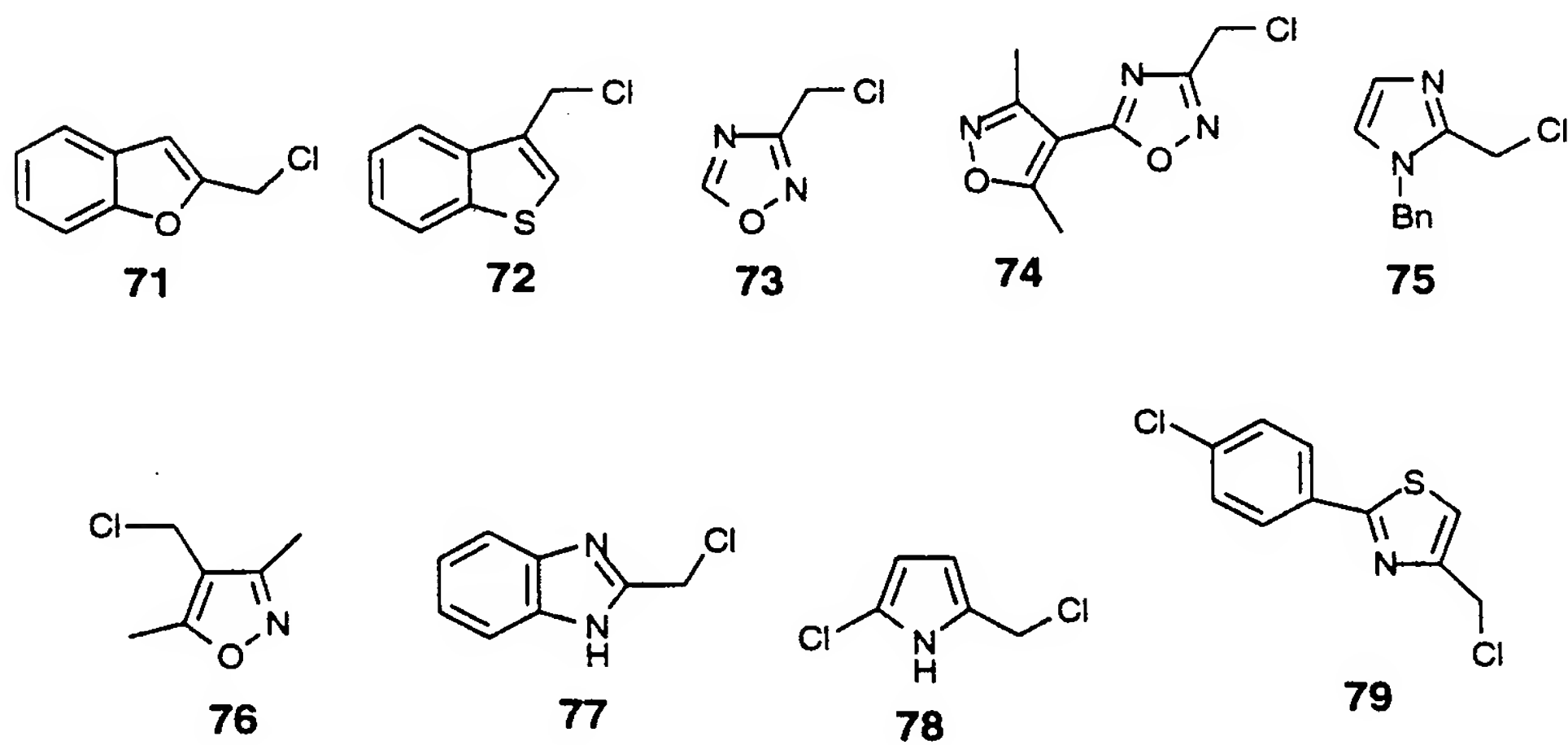
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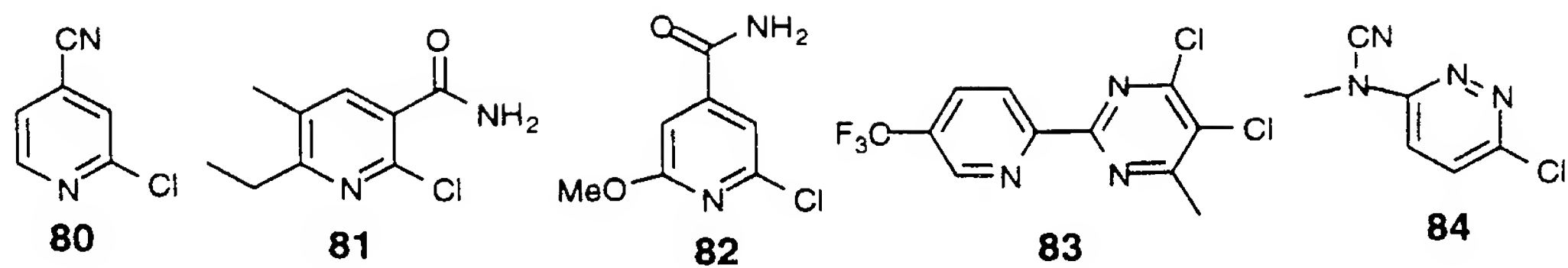


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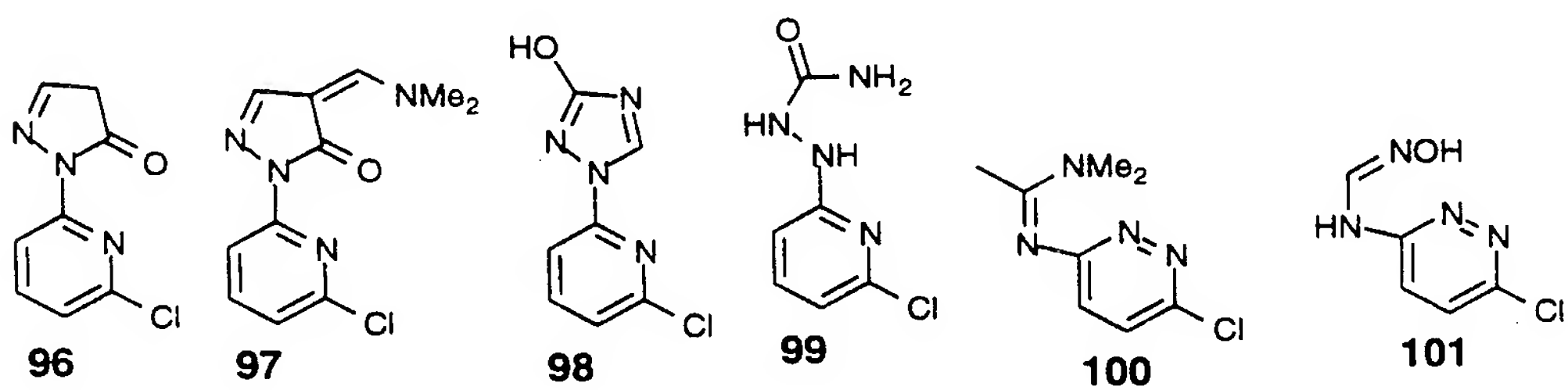
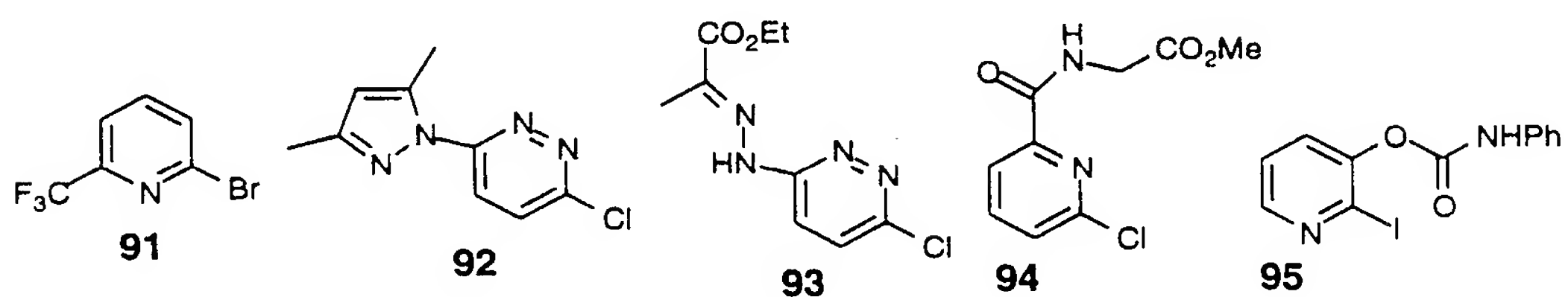
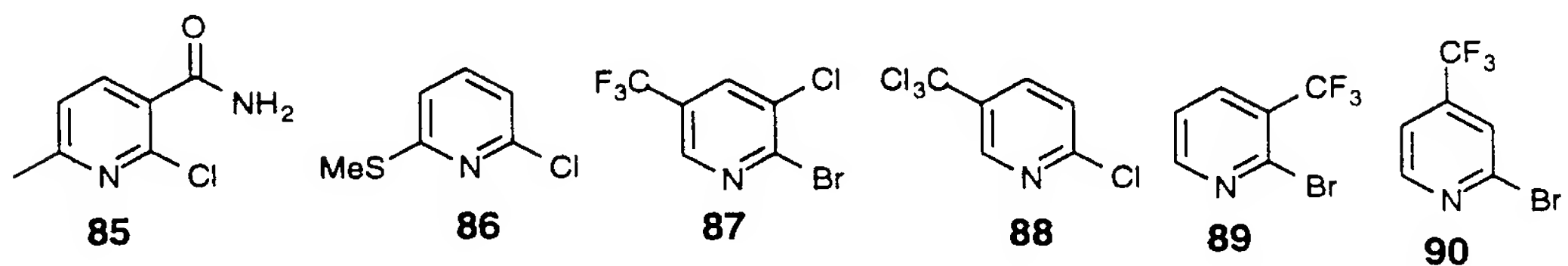


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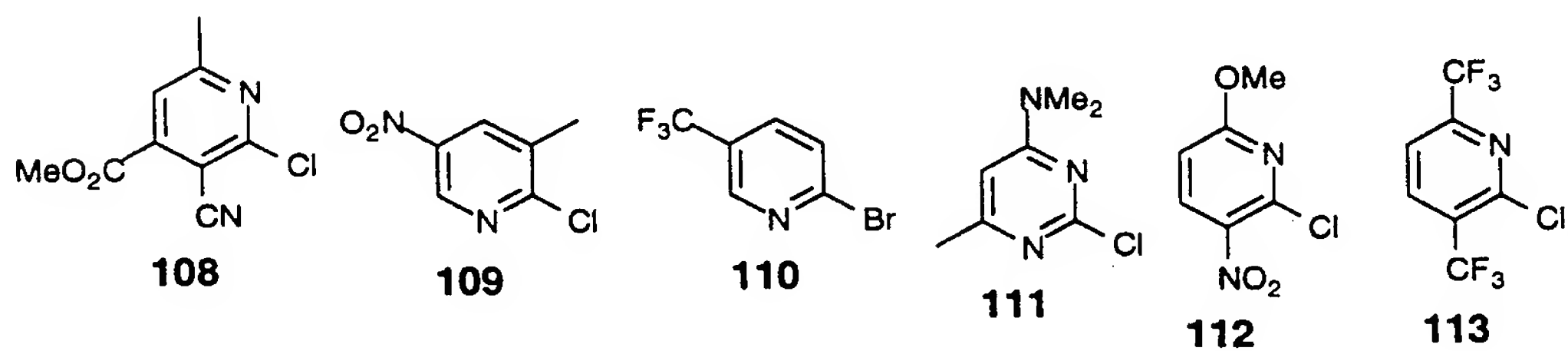
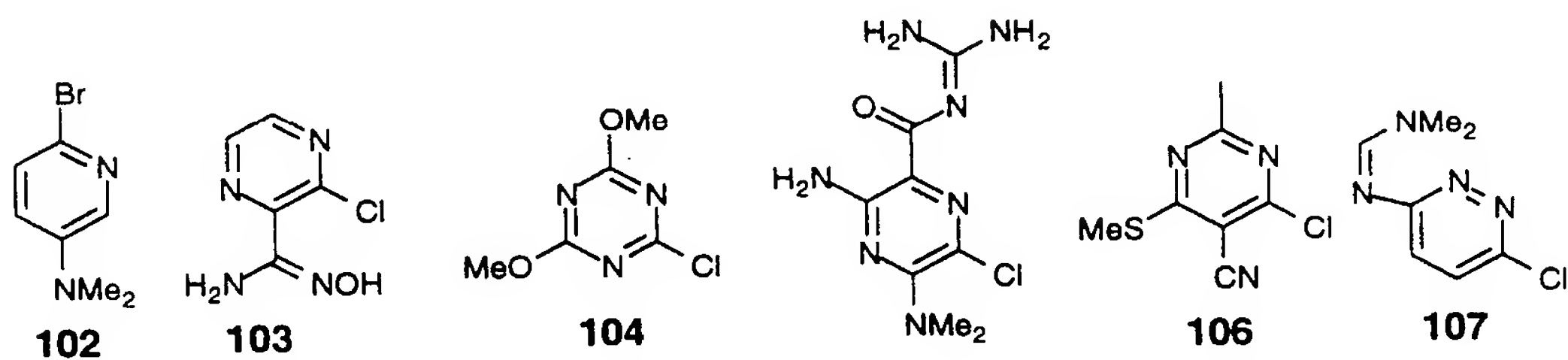




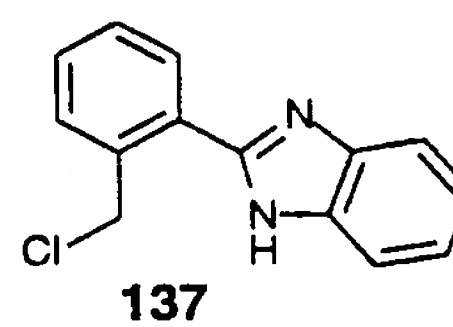
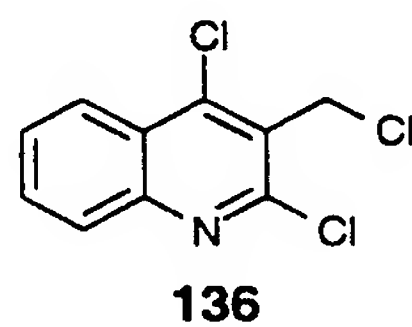
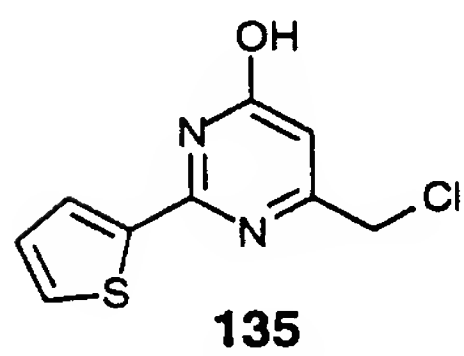
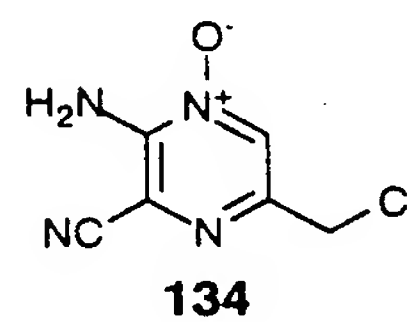
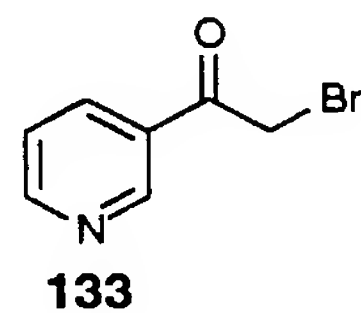
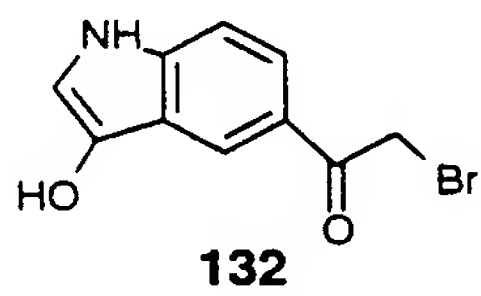
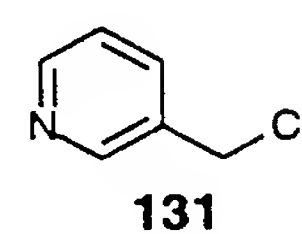
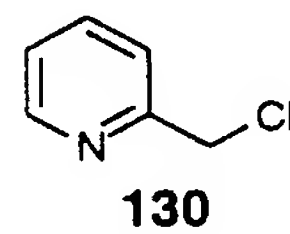
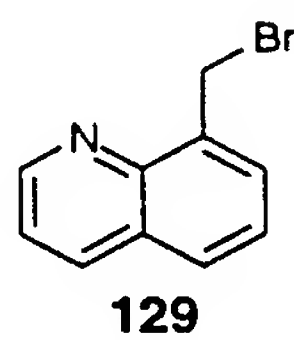
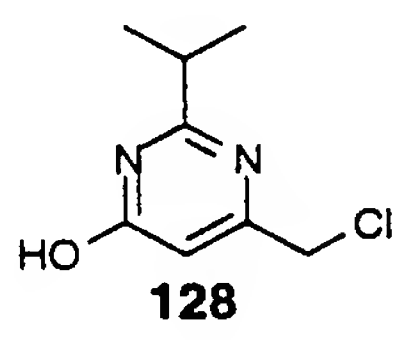
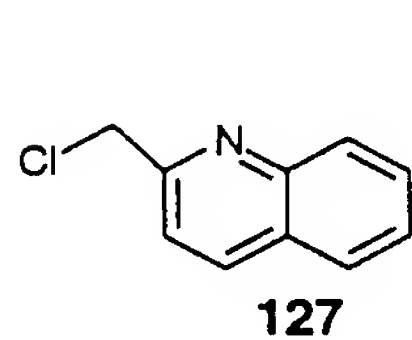
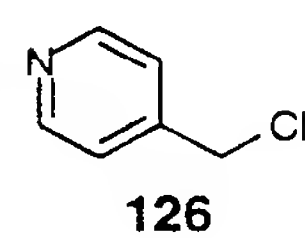
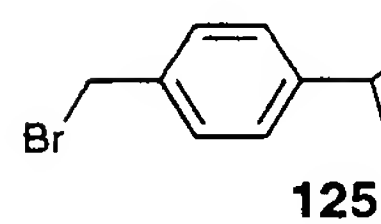
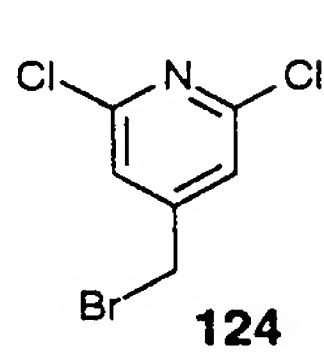
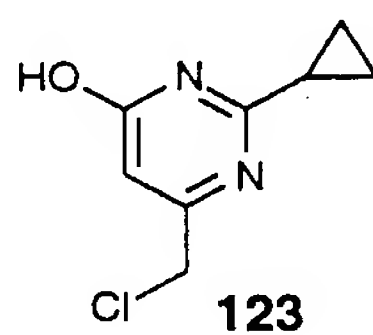
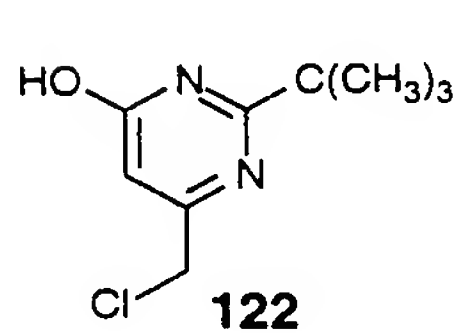
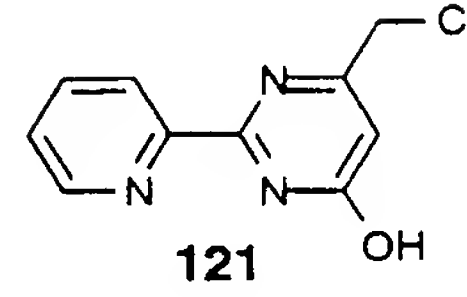
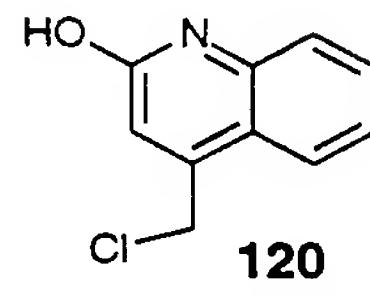
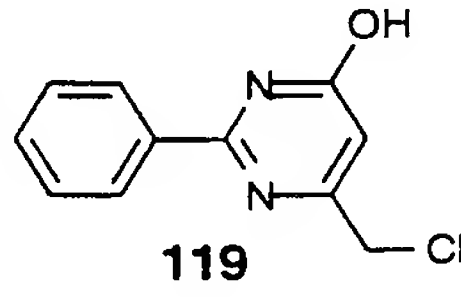
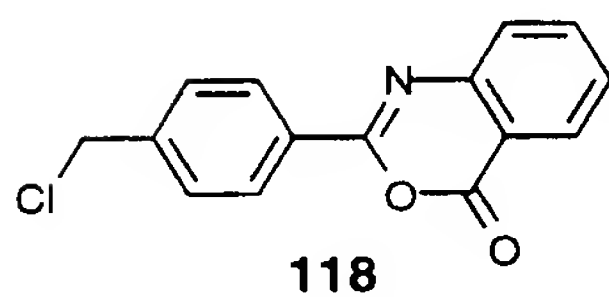
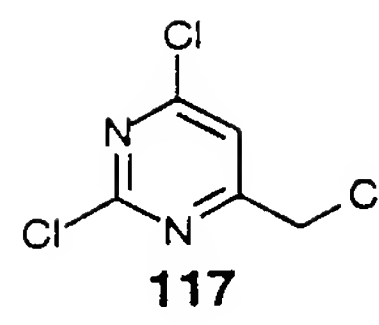
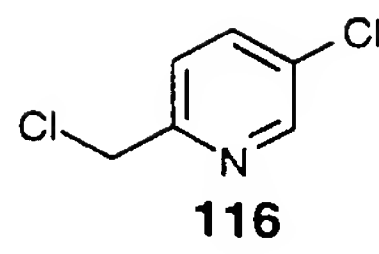
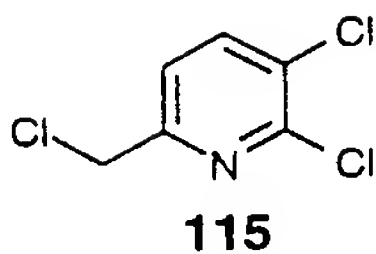
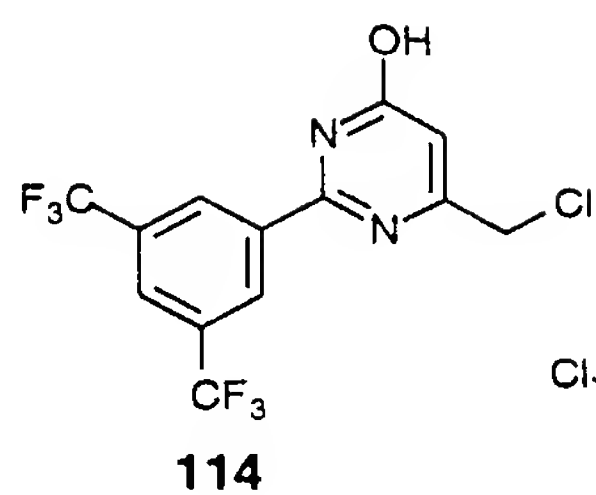
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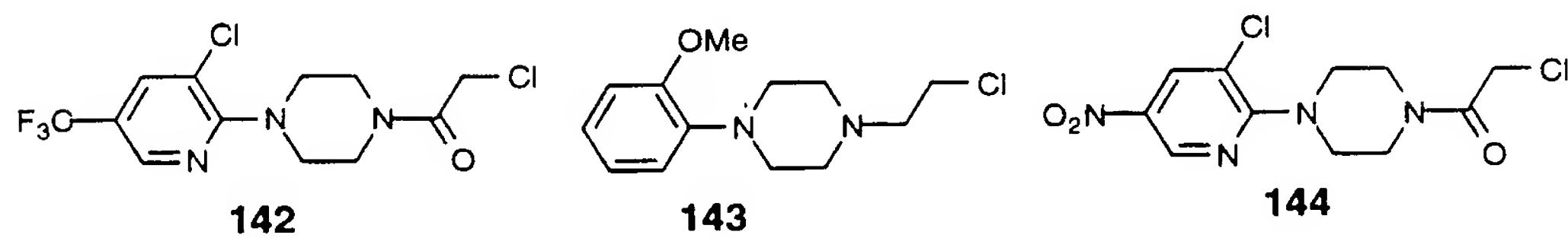
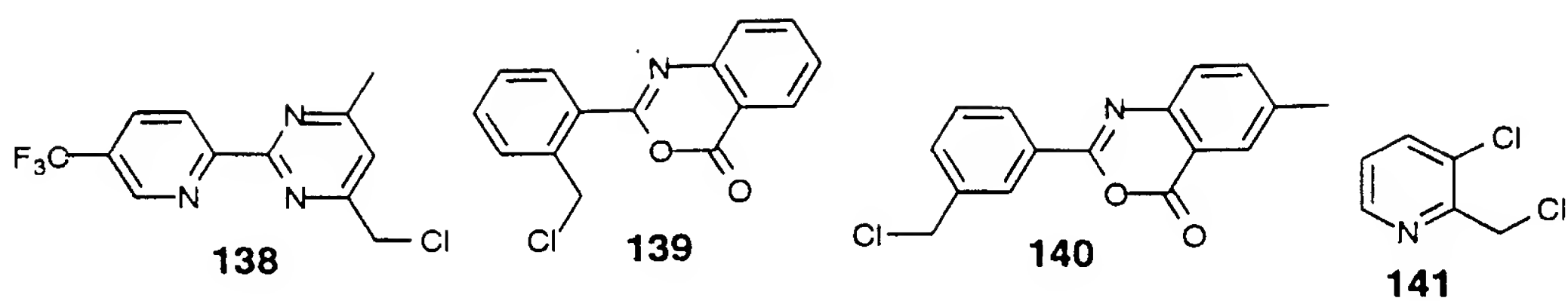
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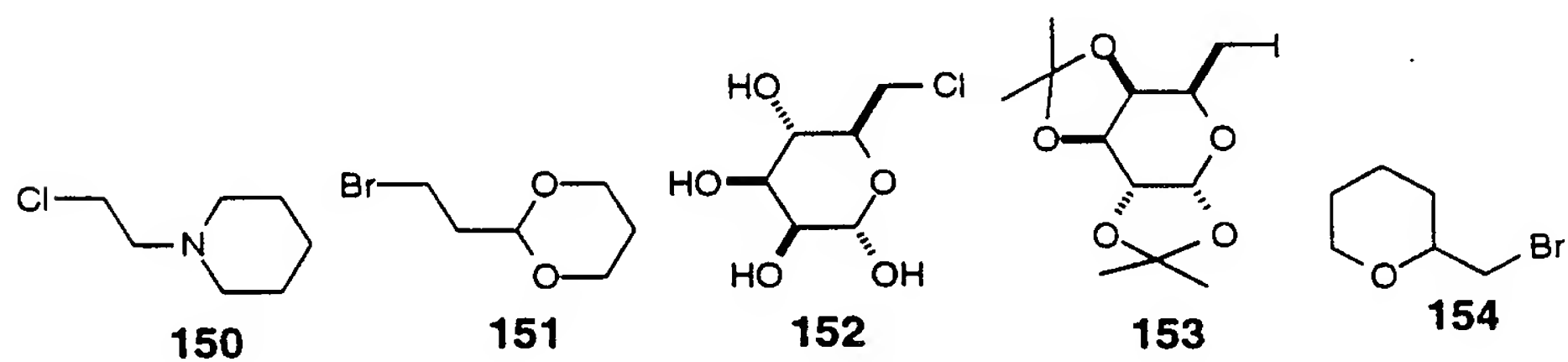
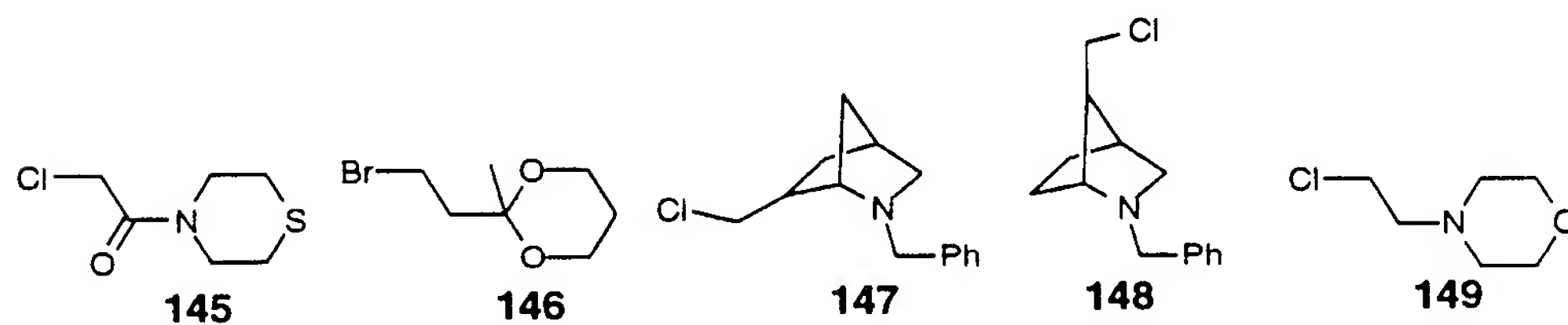
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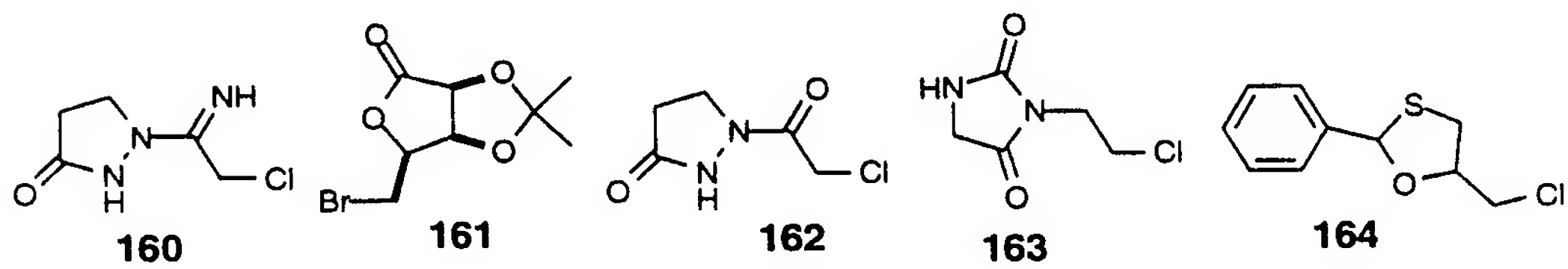
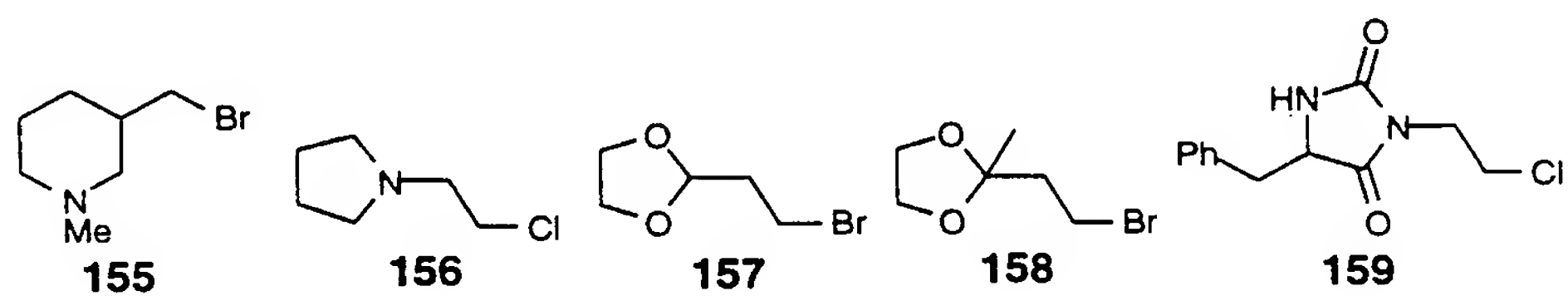


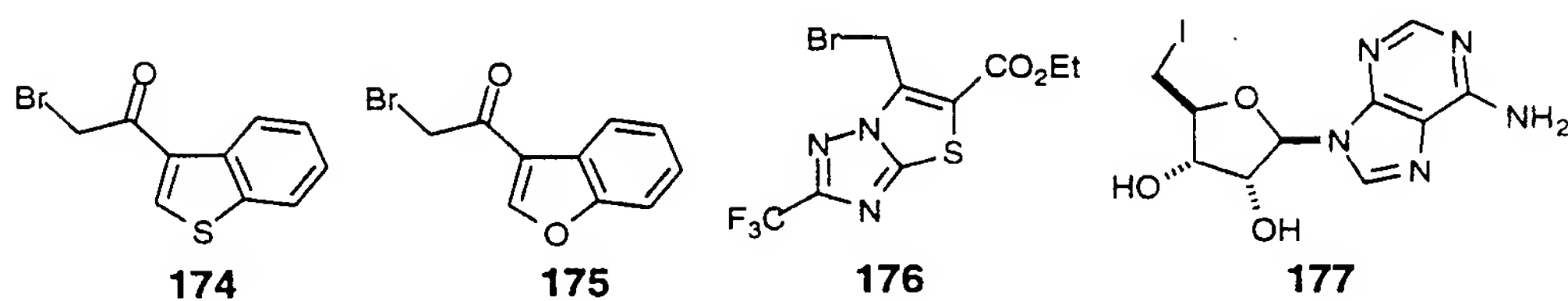
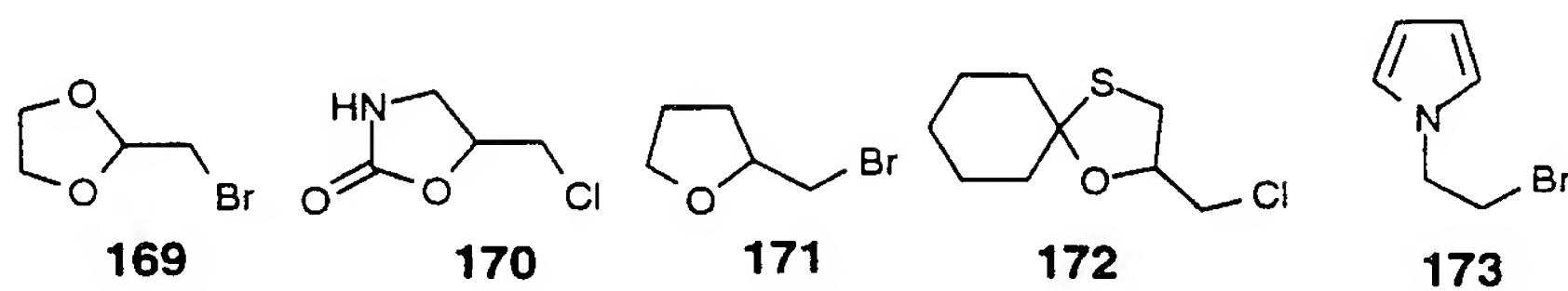
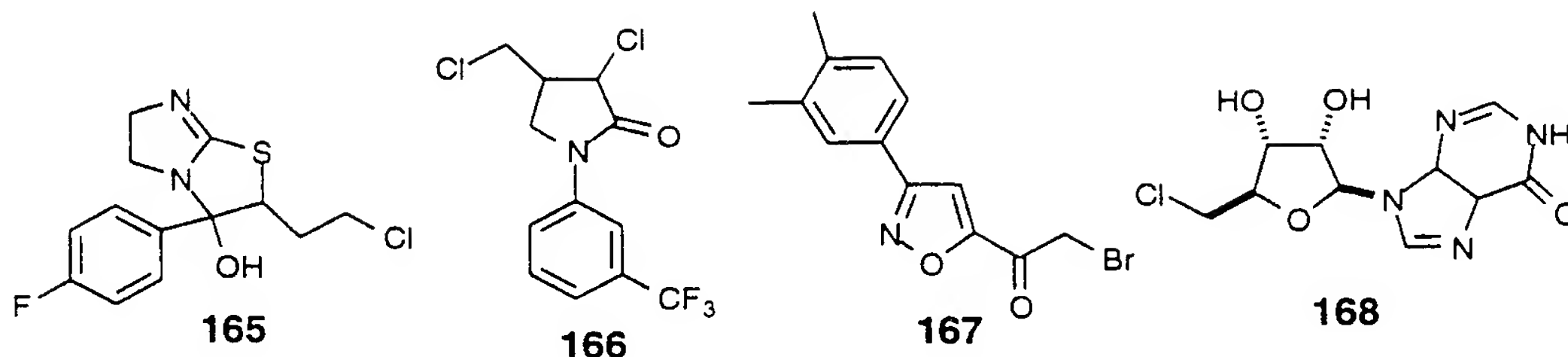


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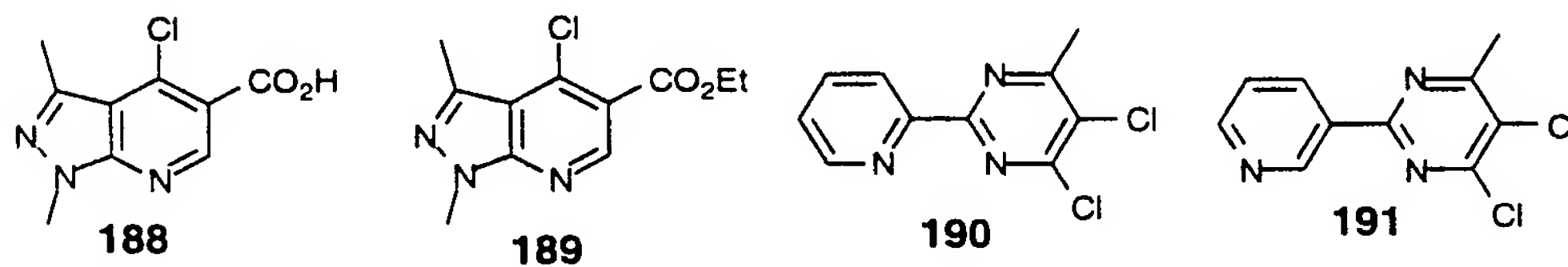
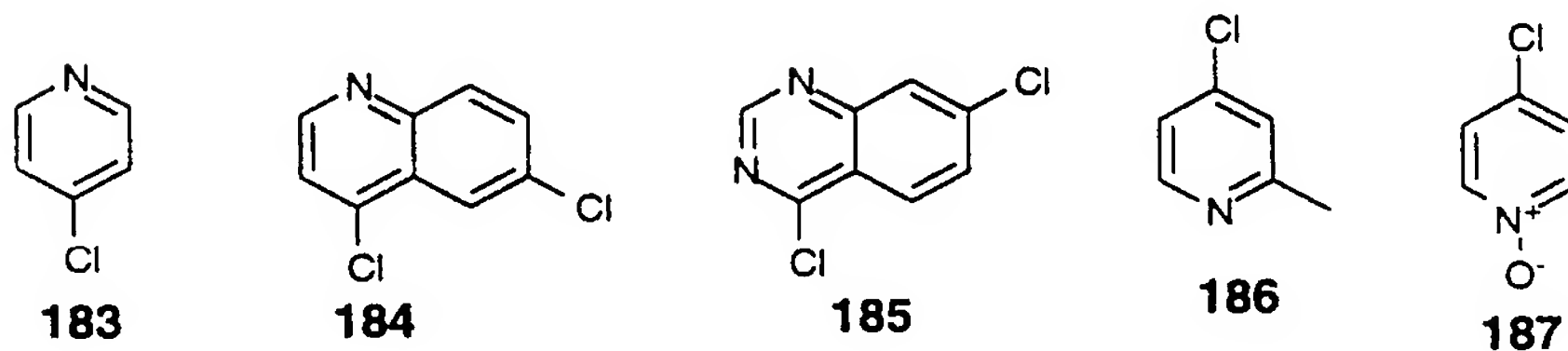
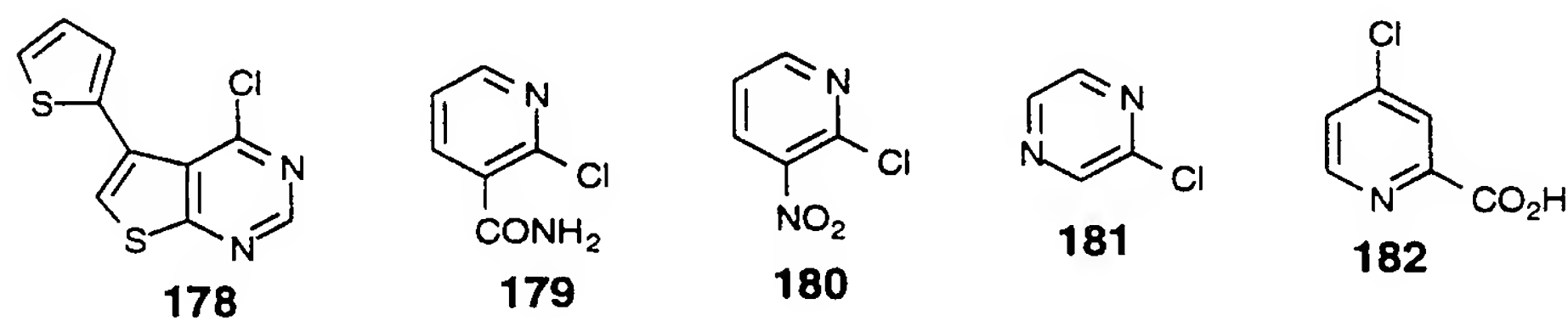


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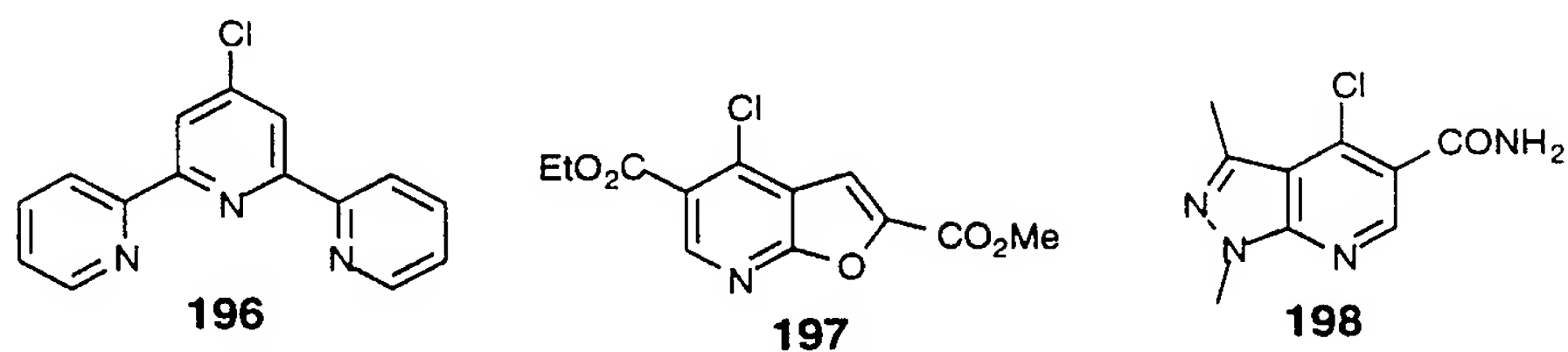
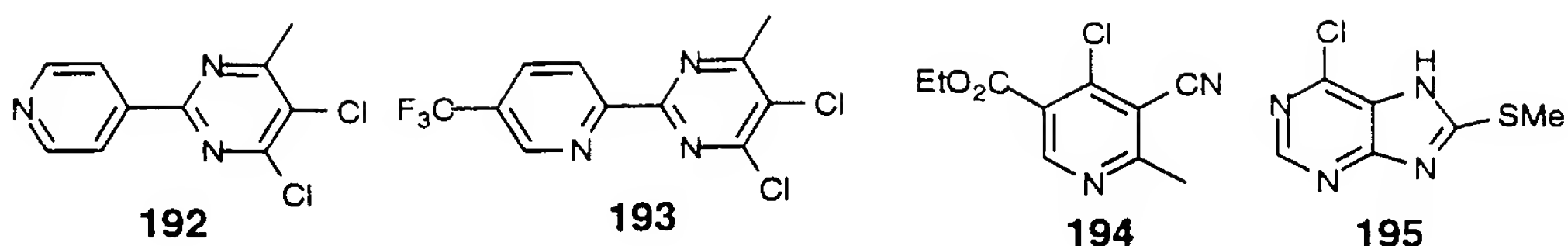




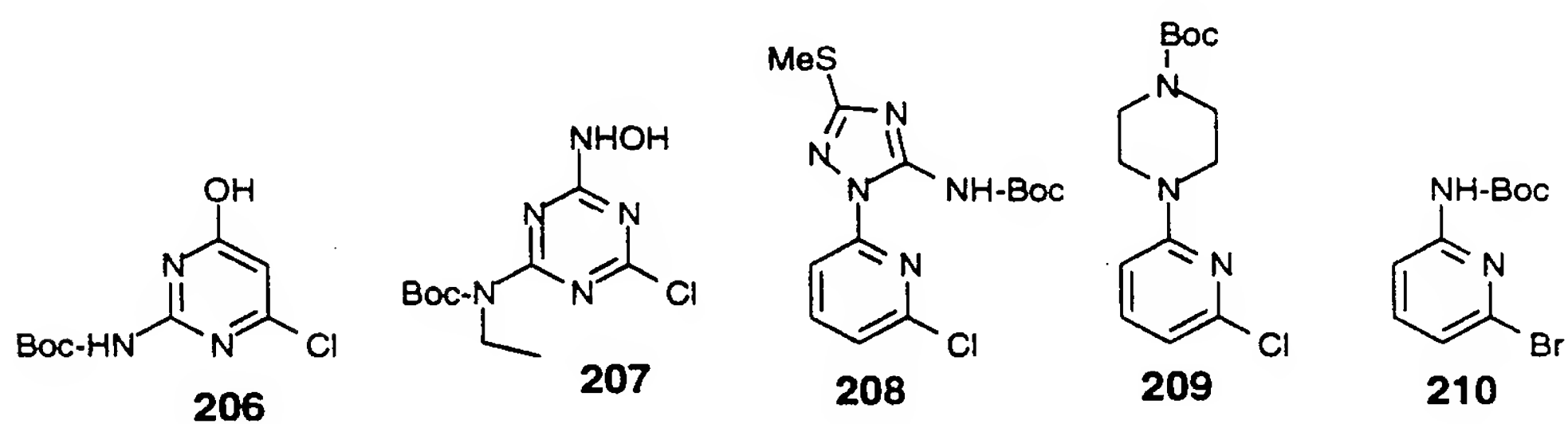
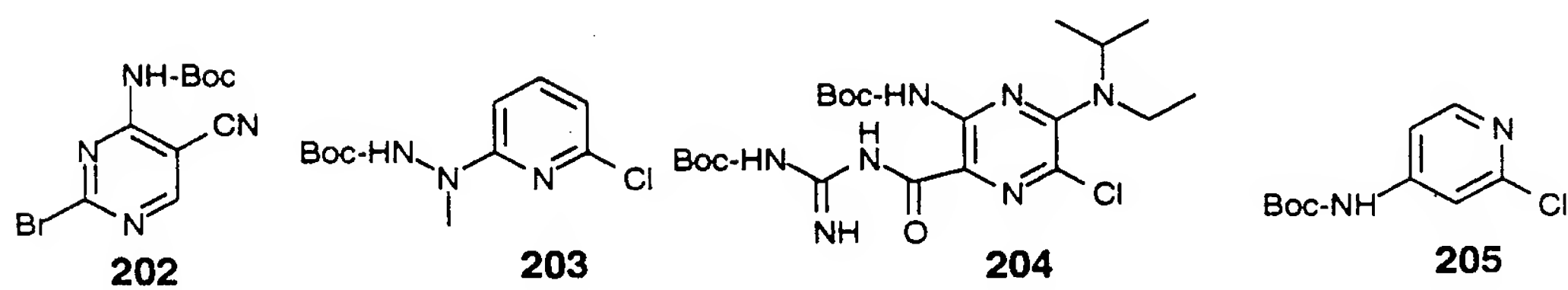
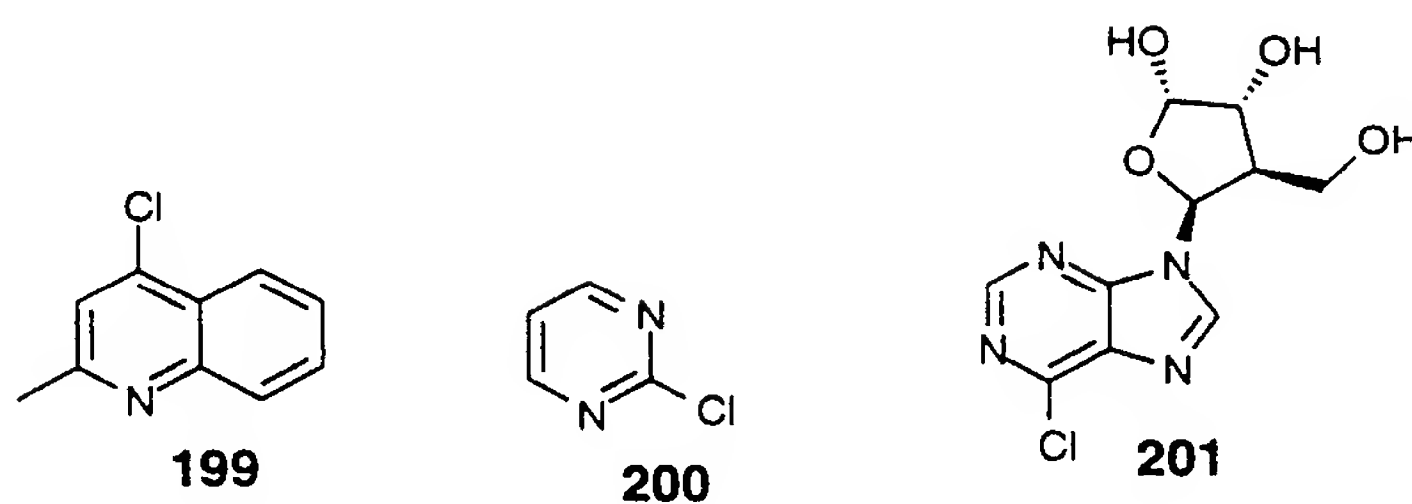
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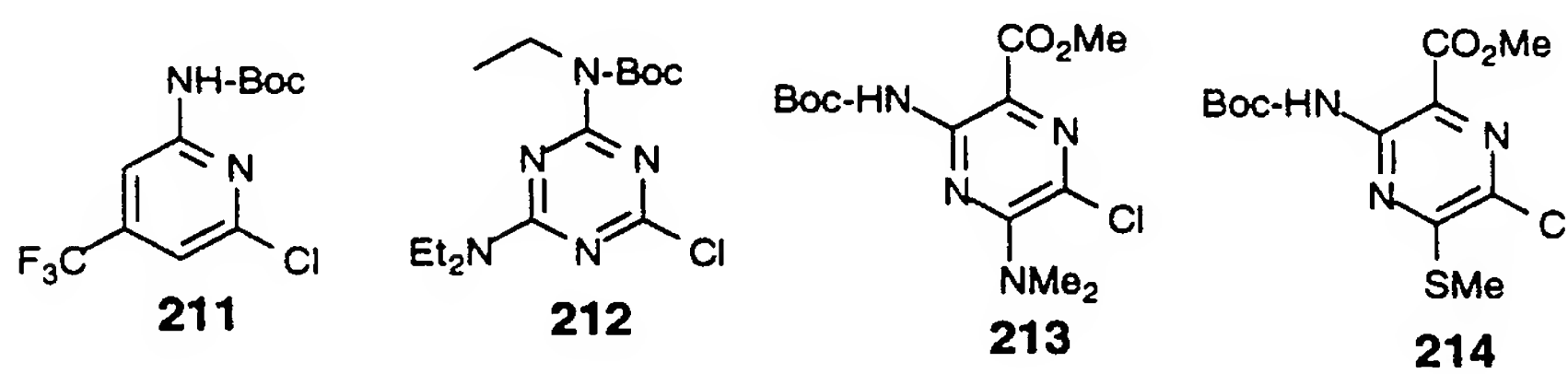
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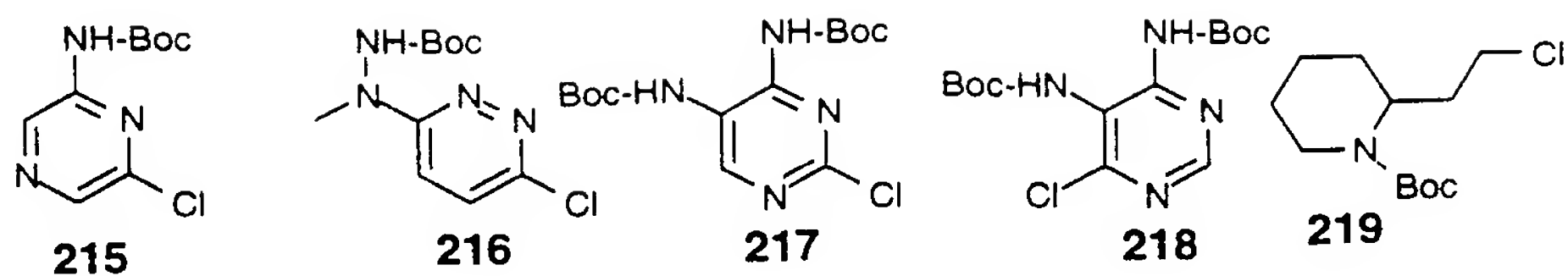


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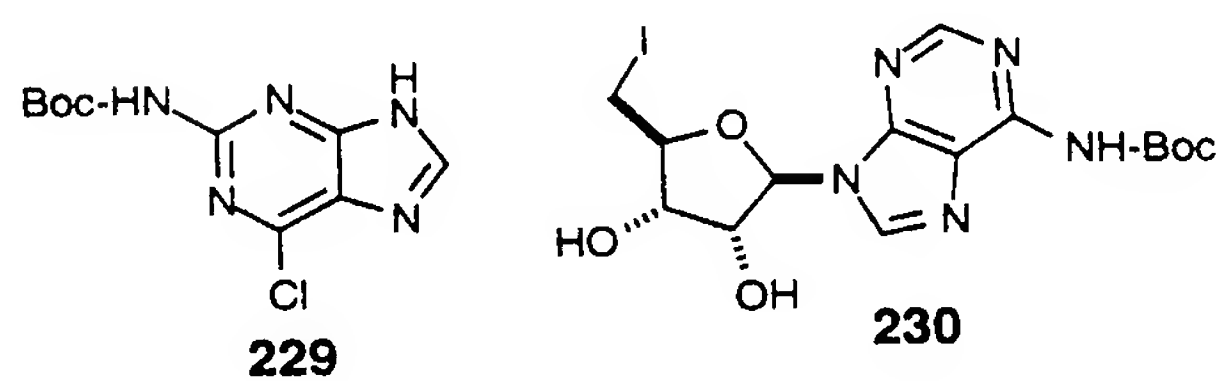
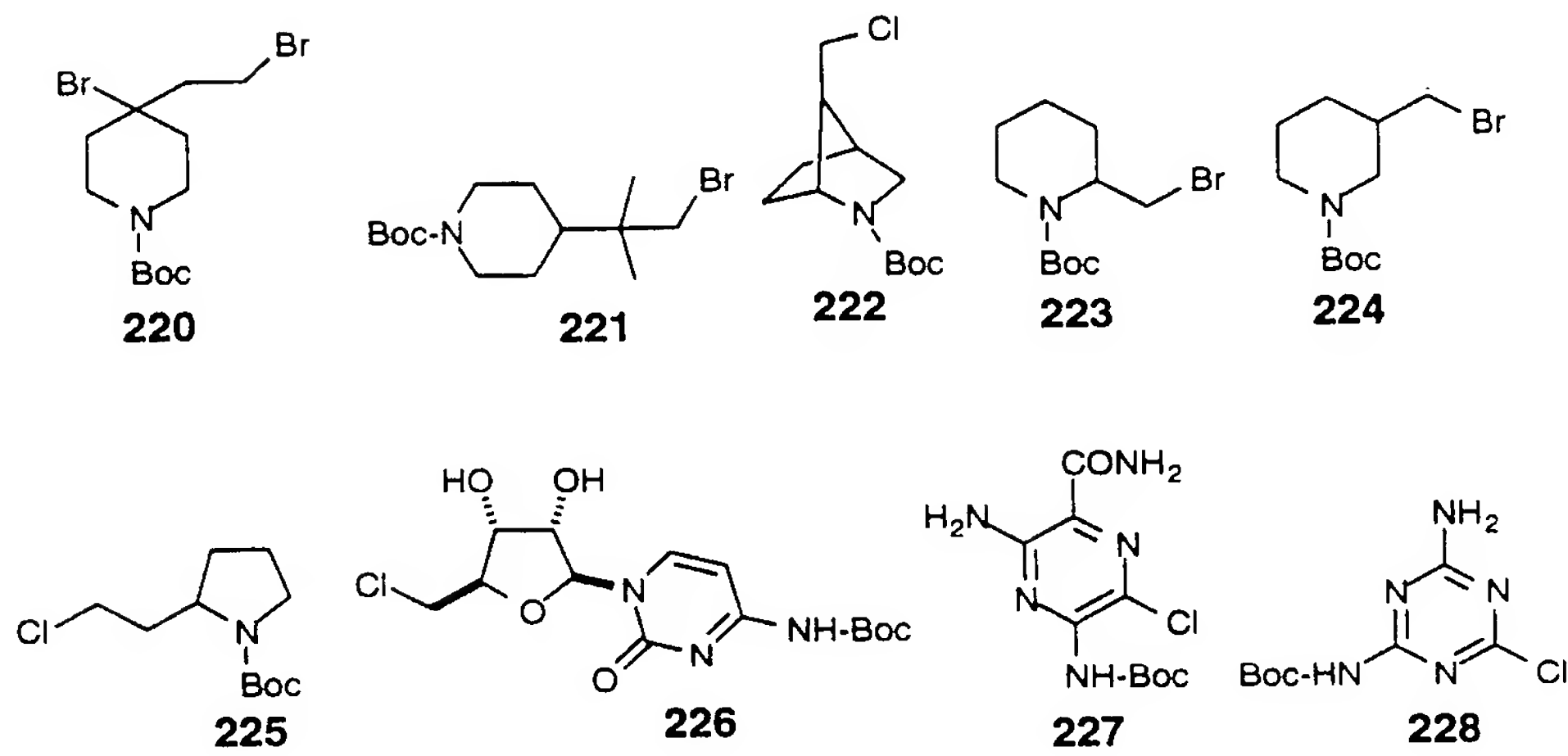


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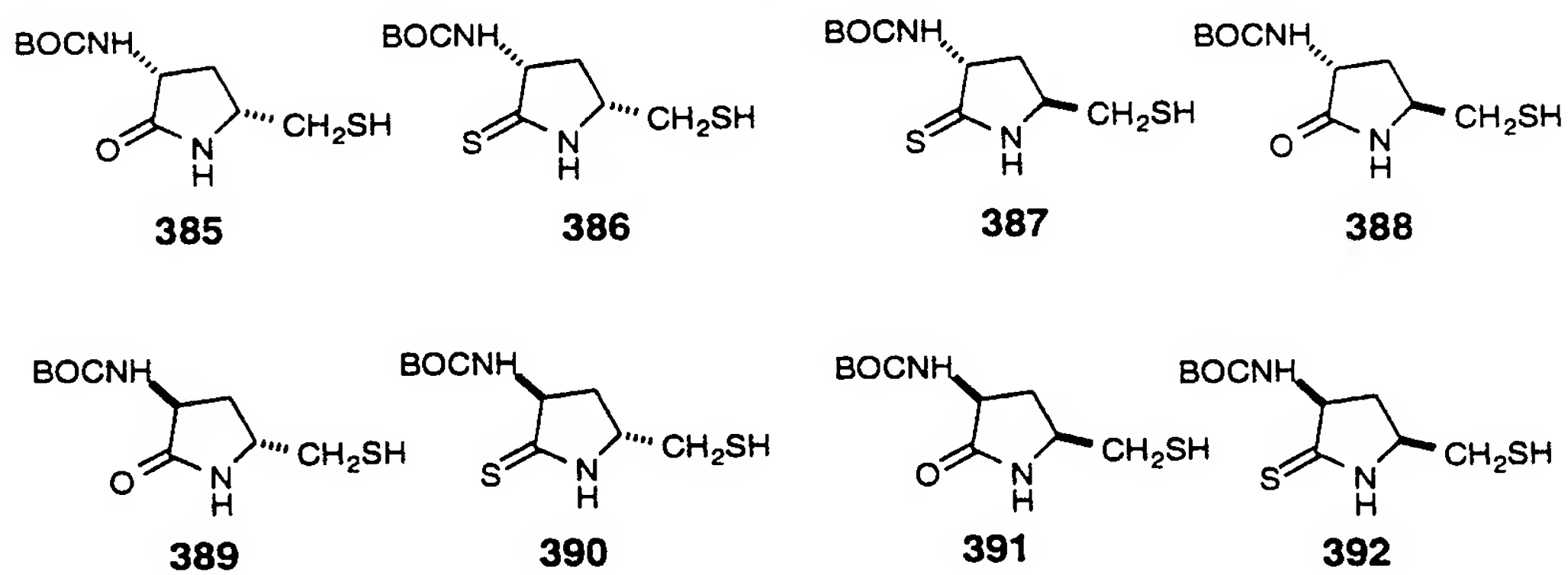




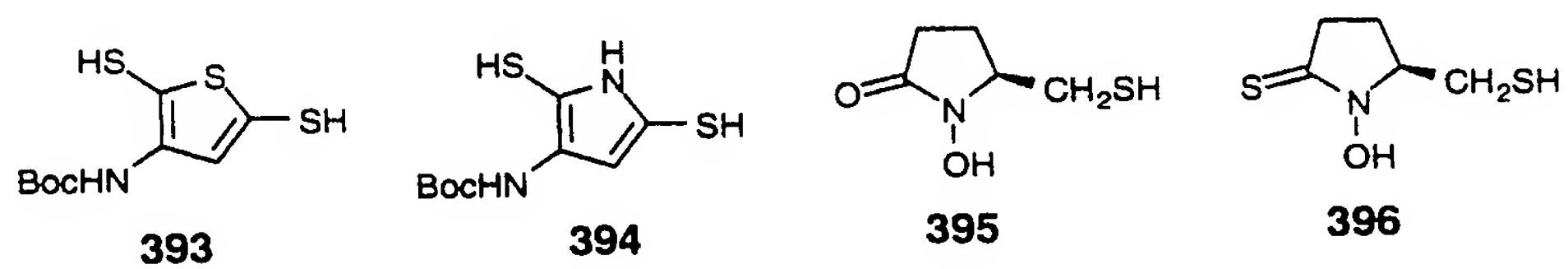
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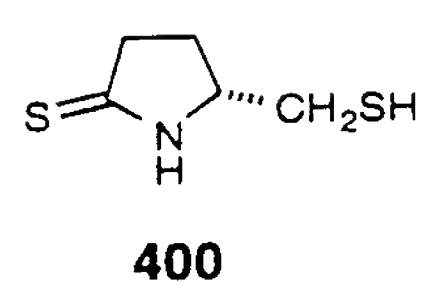
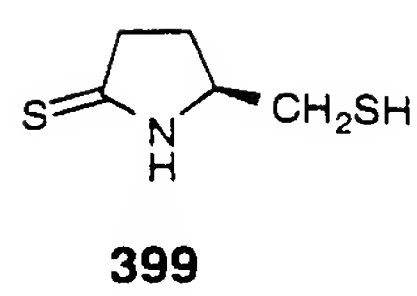
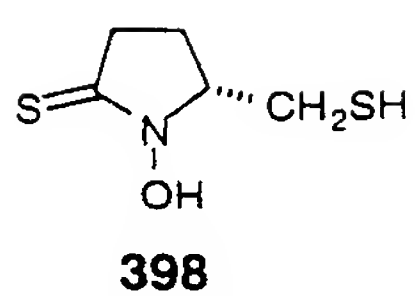
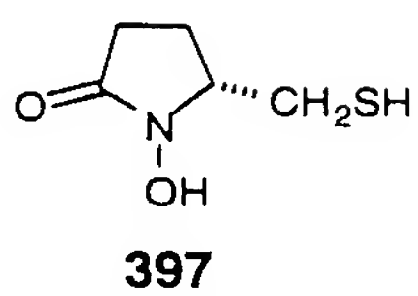


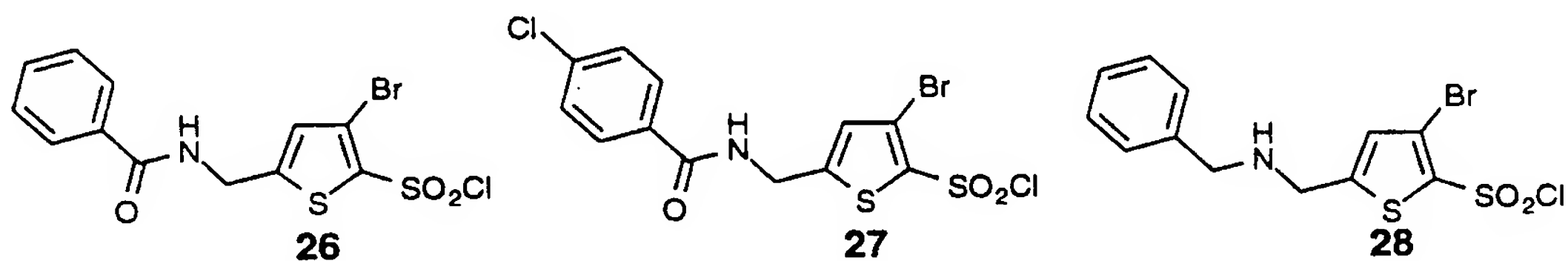
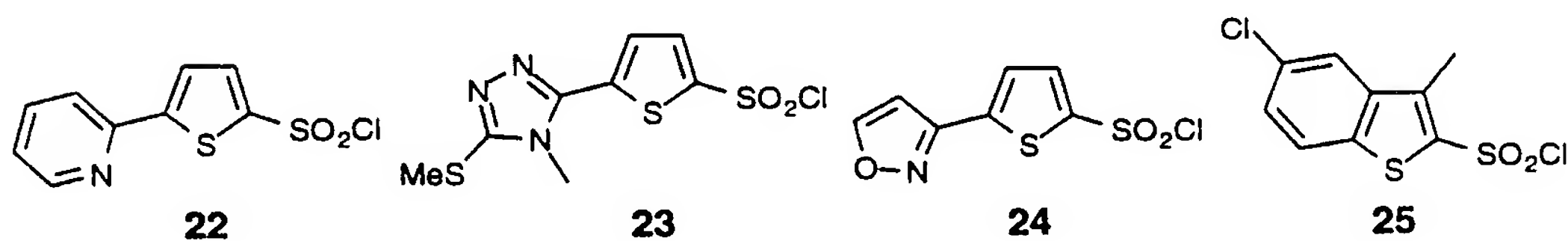
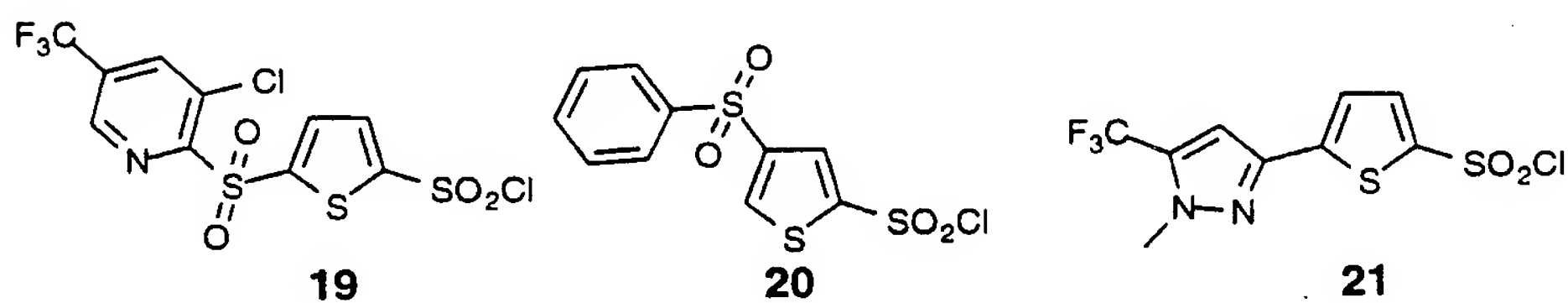
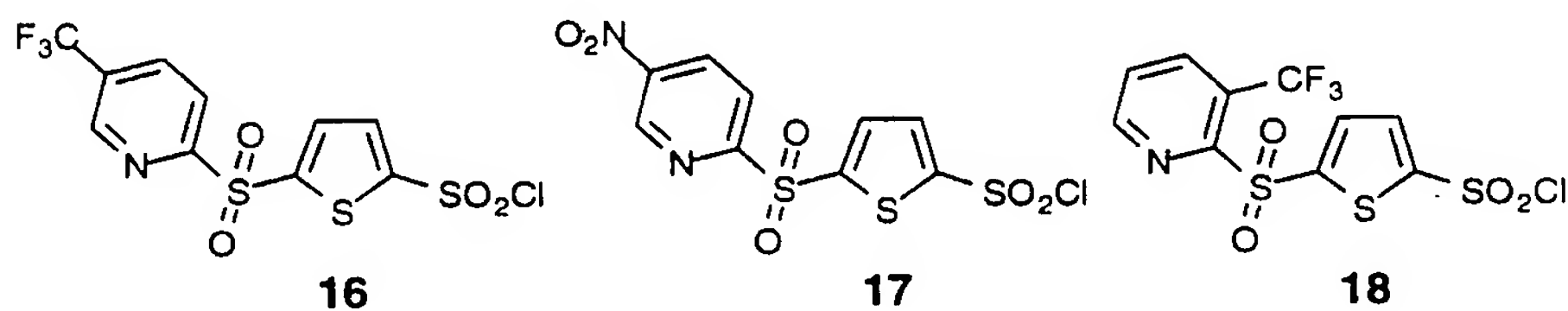
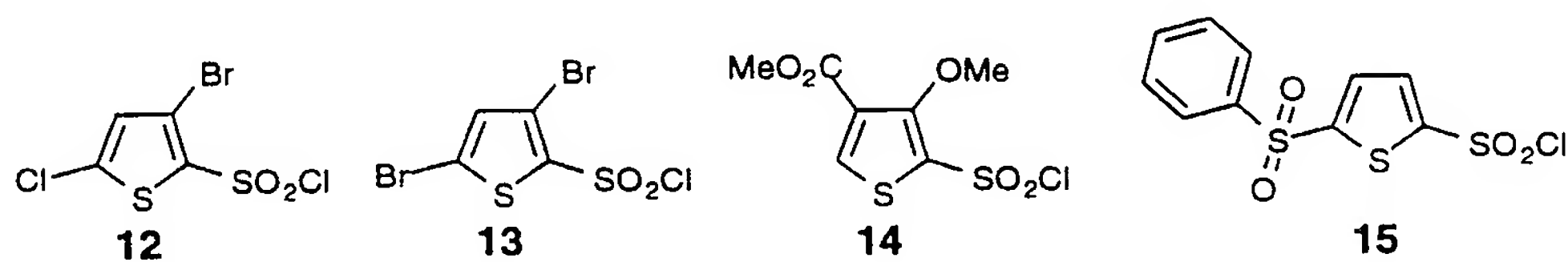
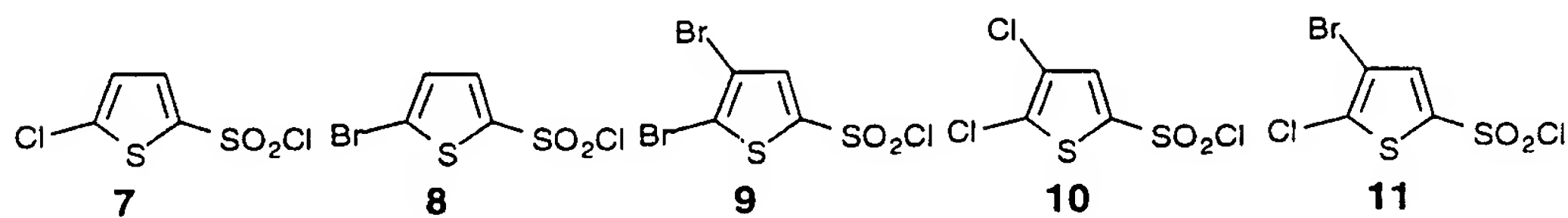
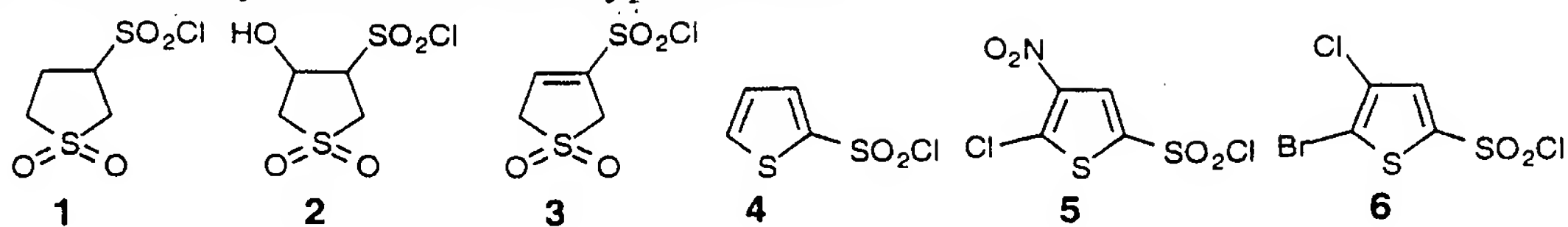
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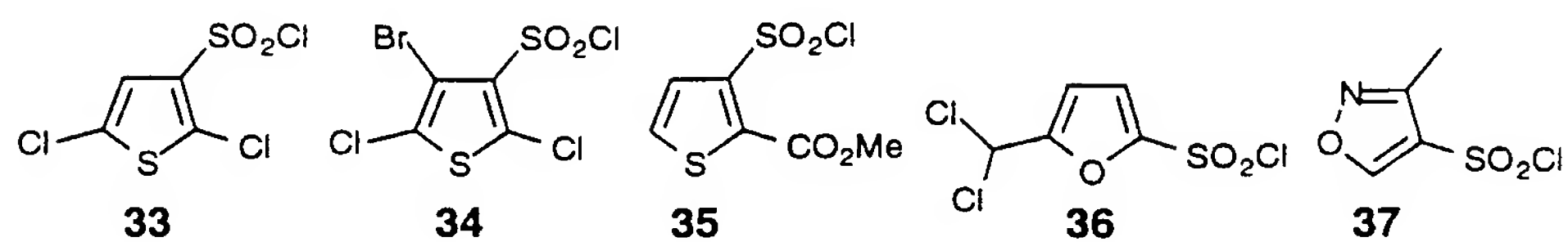
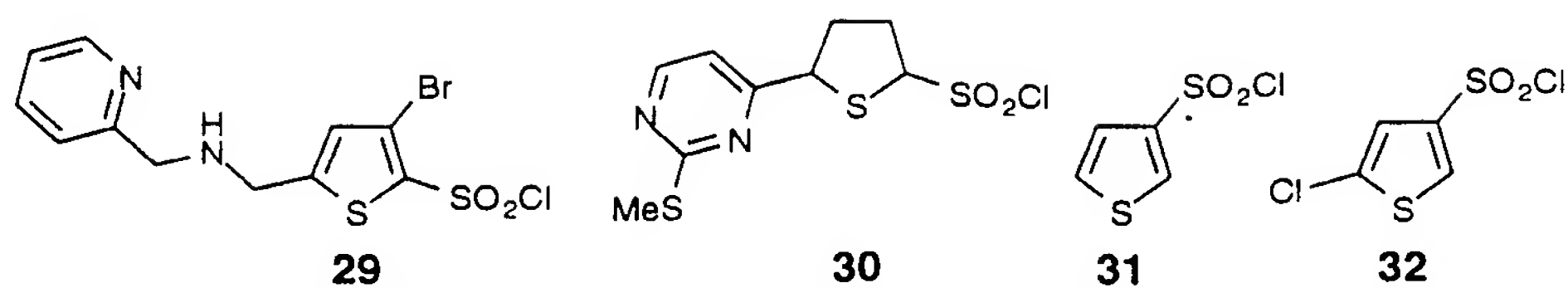
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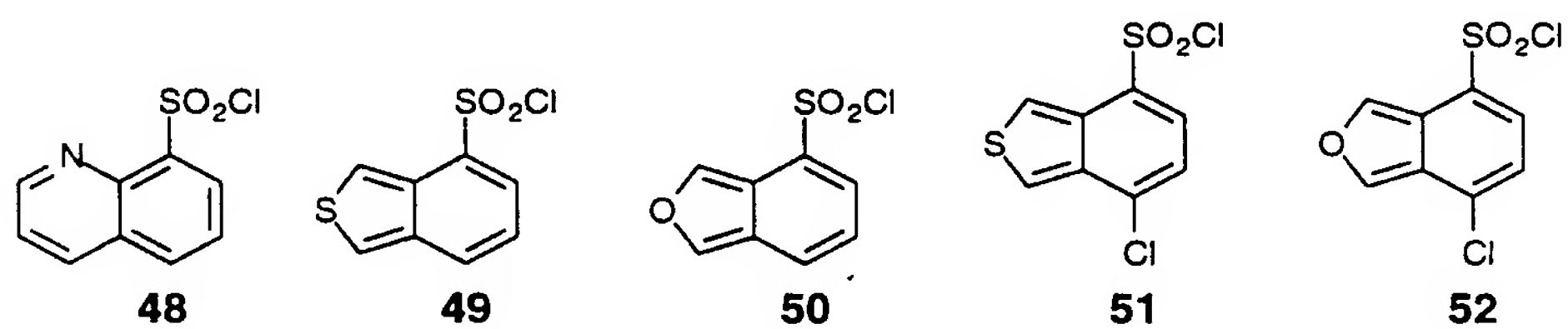
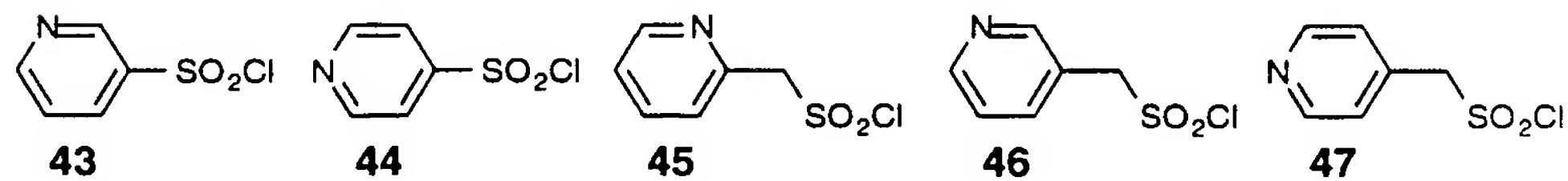
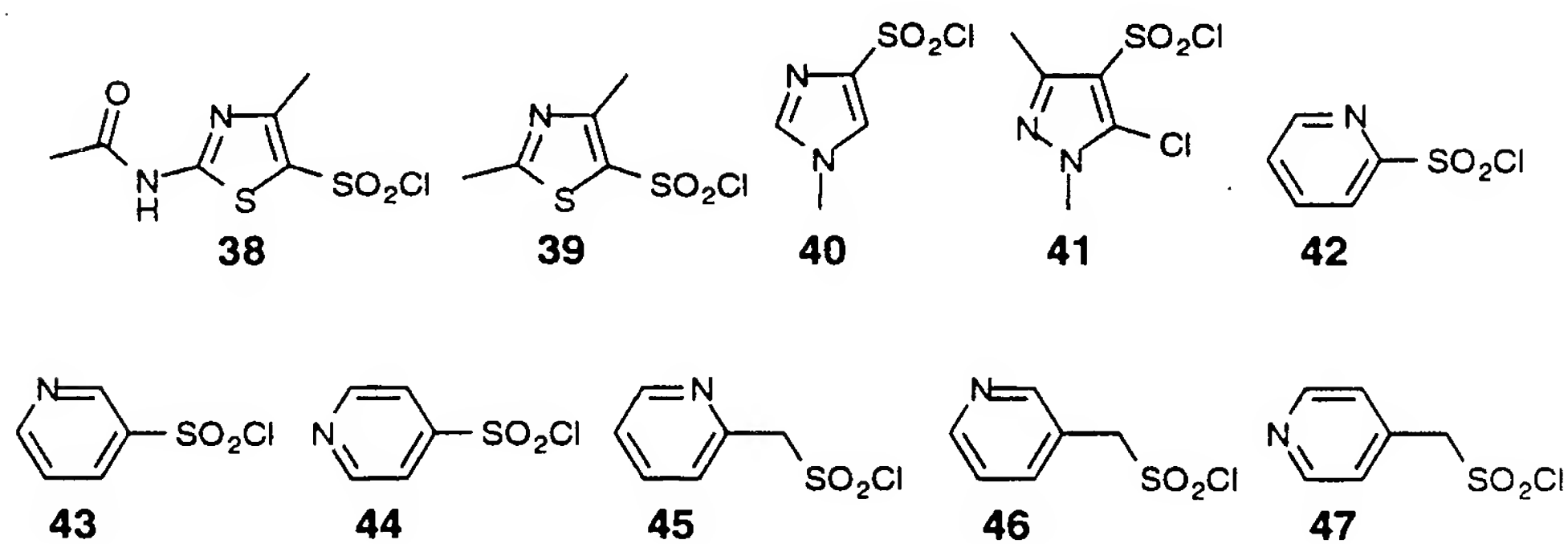


3495 Table 18. Sulfonyl chlorides of the type A-SO<sub>2</sub>Cl

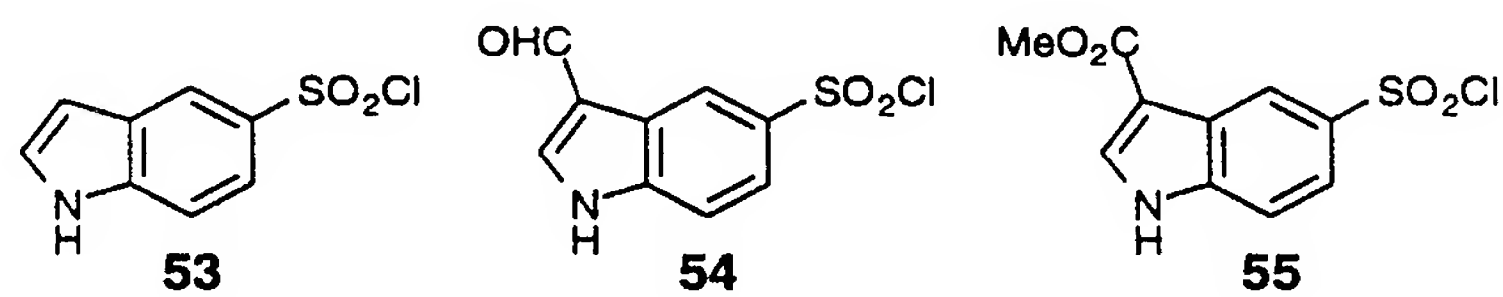
3510



3515



3520



The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

In Tables 2-10, the abbreviation bz=benzoyl, bn=benzyl, Ph=phenyl, BOC=t-butylloxycarbonyl and TS=p-toluenesulfonyl.

Compound 1

(3-(Aminomethyl)benzoyl)-Met-OCH<sub>3</sub>

Step A

(3-(Chloromethyl)benzoyl)-Met-OCH<sub>3</sub>

To a solution of methionine methyl ester hydrochloride (2.0 g, 10 mmol) and 3-(chloromethyl)benzoyl chloride (2.08 g, 11.0 mmol) in methylene chloride (50 mL) was slowly added triethylamine (3.07 mL, 22.0 mmol) at ice bath temperature for 2 hours. The mixture was washed with 0.5 N HCl (50 mL x 2), brine (50 mL x 2) and water (50 mL x 2) then dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to give the desired product (3.03 g) as a white solid: m.p. 82-83°C;

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.82 (1H, s), 7.74 (1H, d, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.42 (1H, t, J=7.7 Hz), 7.06 (1H, br d, J=7.6 Hz), 4.92 (1H, ddd, J=7.6, 7.1, 5.1 Hz), 4.59 (2H, s), 3.78 (3H, s), 2.58 (2H, t, J=7.1 Hz), 2.26 (1H, sm), 2.15 (1H, m), 2.10 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 172.59, 166.54, 138.13, 134.25, 131.95, 129.12, 127.42, 126.97, 52.72, 52.14, 45.55, 31.47, 30.12, 15.55.

Step B

(3-(Azidomethyl)benzoyl)-Met-OCH<sub>3</sub>

A suspension of (3-(chloromethyl)benzoyl)-Met-OCH<sub>3</sub> (1.58 g, 5.0 mmol) and sodium azide (1.3 g, 20.0 mmol) in DMSO (40 mL) was stirred at 80°C for 7 hours. The mixture was diluted with methylene chloride (100 mL), washed with brine (70 mL x 2) and water (70 mL x 2), and then dried over anhydrous MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure to give a yellow residue. Chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product (1.45 g) as a colorless solid: m.p. 48-49°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.78 (2H, m), 7.49 (2H, m), 6.99 (1H, br d, J=7.4 Hz), 4.49 (1H, ddd, J=7.4, 7.1, 5.2 Hz), 4.42 (2H, s), 3.80 (3H, s), 2.60 (2H, t, J=7.4 Hz), 2.29 (1H, m), 2.17 (1H, m), 2.12 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 177.50, 166.54, 135.97, 134.06, 131.18, 128.89, 126.84, 126.71, 54.09, 52.47, 51.95, 31.38, 30.00, 15.30.

Step C



(3-(Aminomethyl)benzoyl)-Met-OCH<sub>3</sub>

A suspension of (3-(azidomethyl)benzoyl)-Met-OCH<sub>3</sub> (1.29 g, 4.0 mmol) and 5%  
3560 palladium on carbon (0.2 g) in methanol (40 mL) was stirred under a hydrogen atmosphere  
(1 atm) for two days at room temperature. The catalyst was removed by filtration through  
celite (1.5 g) and the solvent was evaporated in vacuo. The residue was washed with water  
(5 mL x 2) and dried to give the desired product (1.12 g) as a colorless foam. <sup>1</sup>H NMR  
(CDCl<sub>3</sub>) δ 7.81 (1H, s), 7.68 (1H, d, *J*=7.4 Hz), 7.45 (1H, d, *J*=6.5 Hz), 7.36 (1H, t,  
3565 *J*=7.4 Hz), 4.91 (1H, ddd, *J*=7.3, 7.1, 5.1 Hz), 3.90 (2H, s), 3.77 (3H, s), 3.21 (2H, br  
s), 2.59 (2H, t, *J*=7.4 Hz), 2.20 (1H, m), 2.12 (1H, m), 2.09 (3H, s).

Compound 2(4-(Aminomethyl)benzoyl)-Met-OCH<sub>3</sub>

3570 The title compound is prepared according to the procedure used to prepare Compound 1 but  
replacing 3-(chloromethyl)benzoyl chloride with 4-(chloromethyl)benzoyl chloride.

Compound 3(3-Aminobenzoyl)-Met-OCH<sub>3</sub>

3575 The title compound was prepared according to the procedure described in J. Biol. Chem.  
269 12410-12413 (1994).

Compound 4(4-Aminobenzoyl)-Met-OCH<sub>3</sub>

3580

Step AN-BOC-4-Aminobenzoic acid

4-Aminobenzoic acid (10 g, 72.9 mmol) was placed into a mixture of dioxane (145.8 mL)  
and 0.5 M NaOH (145.8 mL). The solution was cooled to 0°C and di-*t*-butyl dicarbonate  
3585 (23.87 g, 109.5 mmol) was added. The reaction mixture was allowed to warm to room  
temperature and stirred overnight. The next day, the dioxane was removed, the residue was  
made acidic and extracted into ethyl acetate. The ethyl acetate fractions were combined and  
washed with 1N HCl to remove any unreacted starting material. The solution was dried  
over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed in vacuo. The crude material was recrystallized  
3590 from ethyl acetate/hexanes to provide the desired product (12.2 g): m.p. 189-190°C; <sup>1</sup>H  
NMR (CD<sub>3</sub>OD) δ 1.52 (9H, s), 7.49 (2H, d, *J*=8.6 Hz), 7.91 (2H, d, *J*=8.6 Hz), 9.28  
(1H, s); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 28.59, 81.29, 118.54, 125.30, 131.81, 145.70, 155.00,  
169.80; Anal. Calc. for C<sub>12</sub>H<sub>15</sub>NO<sub>4</sub>, C: 60.76, H: 6.37, N: 5.90; Found, C: 60.52, H:  
6.43, N: 5.83; HRMS Calc. for C<sub>12</sub>H<sub>15</sub>NO<sub>4</sub>, 237.0961, Found, 237.1001.

3595

Step B(N-BOC-4-Aminobenzoyl)-Met-OCH<sub>3</sub>

Into a dried, nitrogen filled flask was placed N-BOC-4-aminobenzoic acid (8.77 g, 36.97 mmol) in dry methylene chloride (148 mL) along with methionine methyl ester  
3600 hydrochloride (8.12 g, 40.66 mmol). This solution was cooled in an ice bath and triethylamine (6.7 mL), EDCI (7.80 g, 40.66 mmol) and hydroxybenzotriazole (HOBT, 5.50 g, 40.66 mmol) were added. The mixture was stirred overnight, diluted with more methylene chloride and was extracted three times each with 1 M HCl, 1M NaHCO<sub>3</sub> and water. The methylene chloride was dried over MgSO<sub>4</sub> and the solvent was removed in  
3605 vacuo. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (9.72 g): m.p. 184-185°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.53 (9H, s), 2.06-2.18 (4H, m), 2.23-2.33 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.80 (3H, s), 4.92 (1H, m), 7.45 (2H, d, J=8.7 Hz), 7.77 (2H, d, J=8.7 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 15.59, 28.34, 30.15, 31.64, 52.10, 52.73, 81.20, 117.73, 127.8, 128.33, 141.88, 152.33, 166.50, 172.75;  
3610 Anal. Calc. for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>S, C: 56.53, H: 6.85, N: 7.29; Found, C: 56.47, H: 6.86, N: 7.29; m/z (EI) 382 (M).

Step C(4-Aminobenzoyl)-Met-OCH<sub>3</sub> hydrochloride

3615 N-BOC-4-aminobenzoyl-Met-OCH<sub>3</sub> (3.53 g, 9.59 mmol) was placed into methylene chloride (30-35 mL) and to it was added 3M HCl/EtO<sub>2</sub> (38.4 mL). After standing, a white precipitate formed. After two hours the solution was decanted and the crystals were collected by centrifugation. The crystals were then washed several times with fresh ether and dried overnight on the vacuum pump. Meanwhile, the filtrate was left to stand  
3620 overnight to allow additional product to precipitate. The second fraction was washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 2.87 g: m.p. 158-164°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.10 (3H, s), 2.12-2.29 (1H, m), 2.52-2.71 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.75 (3H, s), 4.79 (1H, m), 7.02 (2H, d, J=8.6 Hz), 7.55 (2H, d, J=8.6 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 15.23, 31.43, 31.53, 52.91, 52.43,  
3625 124.35, 130.56, 135.31, 135.76, 168.95, 173.87; HRMS Calc. for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>S, 282.1038, Found 282.1009.

Compound 5(4-Amino-3-methylbenzoyl)-Met-OCH<sub>3</sub>

3630

Step A

N-BOC-4-Amino-3-methylbenzoic acid

4-Amino-3-methylbenzoic acid (5 g, 33.1 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The  
3635 resulting orange-brown solid was recrystallized from ethyl acetate and hexanes to provide the desired product (4.99 g) as tan prismatic crystals: m.p. 180-182°C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) d 1.51 (9h, s), 2.27 (3H, s), 7.66 (1H, d, *J*=8.1 Hz), 7.79-7.82 (2H, m), 8.32 (1H, s); <sup>13</sup>C NMR (CD<sub>3</sub>OD) d 17.98, 28.62, 81.47, 123.12, 127.05, 129.14, 130.65, 132.99, 142.45, 155.33, 168.70; Anal. Calc. for C<sub>13</sub>H<sub>17</sub>NO<sub>4</sub>, C: 62.15, H: 6.82, N: 5.58; Found  
3640 C: 62.07, H: 6.86, N: 5.46; m/z (EI) 251; HRMS Calc. for C<sub>13</sub>H<sub>17</sub>NO<sub>4</sub>, 251.1158; Found, 251.1153.

Step B(N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH<sub>3</sub>

3645 N-BOC-4-amino-3-methylbenzoic acid (2.00 g, 7.96 mmol) was reacted with with methionine methyl ester hydrochloride (1.75 g, 8.76 mmol), triethylamine (1.4 mL), EDCI (1.68 g, 8.76 mmol) and hydroxybenzotriazole (HOBT, 1.18 g, 8.76 mmol) in dry methylene chloride (31.8 mL) according to the procedure described for the preparation of N-BOC-4-aminobenzoyl)-Met-OCH<sub>3</sub>. The resulting solid was recrystallized from ethyl  
3650 acetate/hexanes to yield the desired product (2.61 g): m.p. 163-165°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) d 1.54 (9H, s), 2.06-2.18 (4H, m), 2.23-2.34 (4H, m), 2.59 (2H, t, *J*=6.8 Hz), 3.80 (3H, s), 4.92 (1H, m), 6.45 (1H, s), 6.88 (1H, d, *J*=7.5 Hz), 7.63 (1H, d, *J*=8.6 Hz), 7.66 (1H, s), 8.05 (1H, d, *J*=8.6 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) d 15.47, 17.61, 28.22, 30.03, 31.55, 51.93, 52.57, 81.04, 118.73, 125.62, 127.66, 129.54, 139.89, 152.34, 166.58,  
3655 172.66.

Step C(4-Amino-3-methylbenzoyl)-Met-OCH<sub>3</sub> hydrochloride

N-BOC-4-Amino-3-methylbenzoyl-Met-OCH<sub>3</sub> (0.99 g, 2.59 mmol) was dissolved in  
3660 methylene chloride (15-20 mL) and precipitated with 3M HCl/Et<sub>2</sub>O (20.7 mL). A pale orange precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.83 g: m.p. 157-159°C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) d 2.04 (3H, s), 2.11-2.25 (1H, m), 2.47 (3H, s), 2.52-2.68 (3H, m), 3.74 (3H, s), 4.75-4.80 (1H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.81 (2H, d, *J*=8.2 Hz), 7.87 (1H, s);  
3665 <sup>13</sup>C NMR (CD<sub>3</sub>OD) d 15.23, 17.28, 31.43, 31.51, 52.91, 53.37, 124.41, 127.85, 131.99, 133.63, 134.14, 135.65, 169.05, 173.84; Anal. Calc. for C<sub>14</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>S, C: 50.52, H: 6.36, N: 8.42; Found C: 50.71, H: 6.40, N: 8.34.

Compound 6

3670

(4-Amino-3-methoxybenzoyl)-Met-OCH<sub>3</sub>Step AN-BOC-4-Amino-3-methoxybenzoic acid

3675

4-Amino-3-methoxybenzoic acid (1 g, 5.98 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting solid was recrystallized from ethyl acetate and hexanes to provide the desired product (1.5 g) as tan crystals: m.p. 176-178°C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.52 (9H, s), 3.92 (3H, s), 7.56 (1H, s), 7.62 (1H, d, *J*=8.4 Hz), 7.96 (1H, s), 8.03 (1H, d, *J*=8.4 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 28.53, 56.35, 81.78, 112.01, 118.58, 124.20, 125.76, 133.84, 149.04, 154.20, 169.60; HRMS Calc. for C<sub>13</sub>H<sub>17</sub>NO<sub>5</sub>, 267.1107; Found, 267.1103.

3680

Step B(N-BOC-4-Amino-3-methoxybenzoyl)-Met-OCH<sub>3</sub>

3685

N-BOC-4-amino-3-methoxybenzoic acid (0.35 g, 1.31 mmol) was reacted with with methionine methyl ester hydrochloride (0.9 g, 1.43 mmol) using EDCI according to the procedure described for the preparation of (N-BOC-4-aminobenzoyl)-Met-OCH<sub>3</sub>.

3690

The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (0.36 g): m.p. 163-165°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.53 (9H, s), 2.09-2.18 (4H, m), 2.23-2.35 (1H, m), 2.60 (2H, t, *J*=6.9 Hz), 3.80 (3H, s), 3.93 (3H, s), 4.92 (1H, br s), 6.93 (1H, d, *J*=7.6 Hz), 7.25 (1H, m), 7.31 (1H, d, *J*=10.2 Hz), 7.44 (1H, s), 8.15 (1H, d, *J*=8.5 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 15.47, 28.23, 30.09, 31.48, 52.06, 52.54, 55.81, 80.82, 98.06, 109.38, 116.66, 119.31, 131.52, 147.23, 152.31, 166.57, 172.58; *m/z* (FAB) 413 (*M* + 1).

3695

Step C(4-Amino-3-methoxybenzoyl)-Met-OCH<sub>3</sub> hydrochloride

3700

N-BOC-4-Amino-3-methoxybenzoyl-Met-OCH<sub>3</sub> (0.71 g, 1.79 mmol) was dissolved in methylene chloride (4 mL) and precipitated with 3M HCl/Et<sub>2</sub>O (12 mL). A reddish precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.55 g: m.p. 176-177°C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.08 (3H, s), 2.21 (2H, m), 2.61 (2H, m), 3.74 (3H, s), 4.02 (3H, s), 4.79 (1H, m), 7.50 (1H, d, *J*=8.2 Hz), 7.57 (1H, d, *J*=4.1 Hz), 7.67 (1H, s); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 15.26, 31.34, 31.42, 52.95, 53.38, 57.12, 112.29, 121.43, 124.57, 124.77, 136.15, 153.67, 168.79, 173.81.

3705

Compound 7  
(4-Amino-1-naphthoyl)-Met-OCH<sub>3</sub>

Step A

3710 4-Amino-1-naphthoic acid

4-Amino-1-naphthalenecarbonitrile (1.5 g, 8.91 mmol) was suspended in a 50% KOH solution (18 mL). The heterogeneous solution was heated at reflux for 2-3 days. Once the solution became homogeneous and TLC showed no more starting material, the deep red solution was cooled and poured over 200 mL of water. The resulting solution was then  
3715 filtered and the desired product was precipitated with concentrated HCl. The resulting red crystals were filtered and the filtrate was refiltered to give pink crystals. The first fraction of crystals was treated with activated carbon to remove some of the red color. A total of 1.51 g of the desired product was obtained: m.p. 169-171°C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 6.69 (1H, d, J=8.2 Hz), 7.38-7.43 (1H, m), 7.48-7.54 (1H, m), 8.03 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.2 Hz), 9.09 (1H, d, J=8.5 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 107.39, 114.61, 122.99,  
3720 123.92, 125.21, 127.40, 128.48, 135.04, 151.35, 171.44; HRMS Calc. for C<sub>11</sub>H<sub>7</sub>NO<sub>2</sub>, 187.0633; Found, 187.0642.

Step B

3725 N-BOC-4-Amino-1-naphthoic acid

4-Amino-1-naphthoic acid (0.86 g, 4.61 mmol) was dissolved in dioxane (9.2 mL). Di-*t*-butyl dicarbonate (1.11 g, 5.07 mmol) was added and the mixture was stirred overnight. The reaction mixture was worked up as described above for N-BOC-4-aminobenzoic acid to give 0.76 g of the desired product as a reddish pink solid: m.p. 194-195°C; <sup>1</sup>H NMR  
3730 (CD<sub>3</sub>OD) δ 1.56 (9H, s), 7.53-7.62 (2H, m), 7.79 (1H, d, J=8.1 Hz), 8.12 (1H, d, J=8.0 Hz), 8.22 (1H, d, J=8.18 Hz), 9.02 (1H, d, J=8.9 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 26.68, 81.62, 119.06, 123.40, 124.57, 127.03, 127.37, 128.49, 128.77, 131.89, 133.76, 139.86, 155.95, 170.73; Anal. Calc. for C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub>, C: 66.90, H: 5.96, N: 4.88; Found C: 66.49, H: 6.08, N: 4.79; m/z (EI), 289; HRMS Calc. for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>, 287.1158;  
3735 Found, 287.1151.

Step C

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH<sub>3</sub>

N-BOC-4-Amino-naphthoic acid (0.46 g, 1.60 mmol), methionine methyl ester  
3740 hydrochloride (0.35 g, 1.76 mmol), EDCI (0.43 g, 1.76 mmol), HOBT (0.24 g, 1.76 mmol) and triethylamine (0.27 mL) in methylene chloride (6.4 mL) were reacted as described above for N-BOC-4-aminobenzoyl-Met-OCH<sub>3</sub>. After workup and



recrystallization from ethyl acetate hexanes, the desired product (0.44 g) was obtained as pale pink crystals: m.p. 131-132°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.57 (9H, s), 2.11-2.21 (4H, m), 2.29-2.41 (1H, m), 2.65 (2H, t, *J*=7.1 Hz), 3.83 (3H, s), 4.99-5.06 (1H, m), 6.68 (1H, d, *J*=8.0 Hz), 7.02 (1H, s), 7.56-7.59 (2H, m) 7.69 (1H, d, *J*=7.9 Hz), 7.87-7.90 (1H, m), 8.02 (1H, d, *J*=7.9 Hz), 8.44-8.48 (1H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 15.56, 28.31, 30.19, 31.65, 52.06, 52.64, 81.17, 115.82, 120.18, 125.79, 126.37, 126.53, 127.18, 131.02, 135.65, 152.93, 169.04, 172.40; HRMS Calc. for C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>S, 432.1719; Found, 432.1702; *m/z* (FAB) 433 (*M*+1).

#### Step D

##### (4-Amino-1-naphthoyl)-Met-OCH<sub>3</sub> hydrochloride

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH<sub>3</sub> (0.57 g, 1.31 mmol) was deprotected with HCl/ether to yield the desired product (0.31 g) as a white solid: m.p. 178-181°C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.08-2.16 (4H, m), 2.20-2.30 (1H, m) 2.57-2.75 (2H, m) 3.82 (3H, s), 4.87-4.91 (1H, m), 7.59 (1H, d, *J*=7.5 Hz), 7.67 (1H, d, *J*=7.5 Hz) 7.71-7.80 (2H, m), 8.03 (1H, dd, *J*=7.1, 2.0 Hz), 8.35 (1H, dd, *J*=6.8, 1.8 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 15.23, 31.40, 53.01, 53.33, 119.90, 122.20, 126.15, 127.41, 127.77, 129.09, 129.31, 131.50, 132.33, 135.64, 171.77, 173.83; *m/z* (FAB), 369 (*M*+1).

#### Compound 8

##### (4-Amino-2-phenylbenzoyl)-Met-OCH<sub>3</sub>

3765

#### Step A

##### 4-Nitro-2-phenyltoluene

2-Bromo-4-nitrotoluene (2.16 g, 10.00 mmol) and phenylboric acid (1.46 g, 12.00 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Pd(Ph<sub>3</sub>P)<sub>4</sub> (0.58 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et<sub>2</sub>O. The crude product was chromatographed on silica gel using hexanes as eluent. After recrystallization from ethanol, the desired product (1.23 g) was obtained as pale orange needles: m.p. 69-71°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.36 (3H, s), 7.29-7.40 (2H, m), 7.41-7.49 (5H, m), 8.07-8.10 (2H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 20.68, 121.96, 124.51, 127.78, 128.41, 128.83, 131.06, 139.06, 139.44, 142.97, 143.48, 146.05; Anal. Calc. for C<sub>13</sub>H<sub>11</sub>NO<sub>2</sub>, C: 73.26, H: 5.20, N: 6.57; Found, C: 73.10, H: 5.12, N: 6.50; *m/z* (EI) 213; HRMS Calc. for C<sub>13</sub>H<sub>11</sub>NO<sub>2</sub>, 213.0790; Found, 213.0793.

#### Step B

3780

4-Nitro-2-phenylbenzoic acid

4-Nitro-2-phenyltoluene (0.5 g, 2.34 mmol) was dissolved in water (4.6 mL) and pyridine (2.3 mL). The mixture was heated to reflux and  $\text{KMnO}_4$  (1.85 g, 11.7 mmol) was added. The reaction mixture was heated overnight and the solution was filtered and washed several times with boiling water. The aqueous solution was made acidic and the product was  
3785 extracted into ethyl acetate. The ethyl acetate solution was dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed in vacuo to provide the desired product (0.37 g): m.p. 174-176°C,  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.38-7.48 (5H, m), 7.96 (1H, d,  $J=8.5$  Hz), 8.21 (1H, d,  $J=2.3$  Hz), 8.28 (1H, dd,  $J=8.48, 2.37$  Hz);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  122.95, 126.09, 129.27, 129.42, 129.49, 131.56, 139.26, 140.42, 144.41, 150.17, 170.52; m/z (EI) 243 (M).

3790

Step C(4-Nitro-2-phenylbenzoyl)-Met-OCH<sub>3</sub>

3795

4-Nitro-2-phenylbenzoic acid (0.3 g, 1.23 mmol), methionine methyl ester hydrochloride salt (0.27 g, 1.35 mmol), EDCI (0.26 g, 1.35 mmol), HOBT (0.18 g, 1.35 mmol) and  
triethylamine (0.19 mL) in dry methylene chloride (4.9 mL) were reacted according the procedure described above for (N-BOC-4-aminobenzoyl)-Met-OCH<sub>3</sub>. After  
recrystallization of the product from ethyl acetate hexanes, the desired product (0.41 g) was obtained: m.p. 98-101°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.62-1.73 (1H, m), 1.79-1.88 (1H, m), 1.91 (3H, s), 1.99 (2H, t,  $J=7.2$  Hz), 3.59 (3H, s), 4.53 (1H, m), 6.45 (1H, d,  $J=7.8$   
3800 Hz), 7.33-7.40 (5H, m), 7.67 (1H, d,  $J=8.3$  Hz), 8.07-8.12 (2H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.92, 29.11, 30.67, 51.51, 52.29, 121.86, 124.74, 128.27, 128.60, 128.69, 129.52, 137.50, 140.56, 141.02, 148.09, 167.23, 171.23; m/z (FAB), 389 (M+1).

Step D

3805

(4-Amino-2-phenylbenzoyl)-Met-OCH<sub>3</sub>

(4-Nitro-2-phenylbenzoyl)-Met-OCH<sub>3</sub> (0.35 g, 0.90 mmol) was dissolved in ethyl acetate (9.0 mL). To this mixture was added  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (1.02 g, 4.5 mmol) and the reaction mixture was heated under nitrogen at reflux for one hour. The mixture was poured onto ice, the solution was made basic using  $\text{NaHCO}_3$  and the product was extracted into ethyl acetate  
3810 several times (7-8). The ethyl acetate solutions were combined, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed in vacuo to the desired product (0.24 g) as a yellow solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.58-1.70 (1H, m), 1.80-1.92 (1H, m), 1.98 (3H, s), 2.06 (2H, t,  $J=7.7$  Hz), 3.62 (3H, s), 4.00 (2H, br s), 4.56-4.63 (1H, m), 5.84 (1H, d,  $J=7.7$  Hz), 6.50 (1H, s), 6.61 (1H, d,  $J=8.4$  Hz) 7.29-7.42 (5H, m), 7.58 (1H, d,  $J=8.3$   
3815 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.02, 29.25, 31.25, 51.57, 52.15, 113.27, 115.88, 123.52, 127.56, 128.37, 128.44, 130.92, 140.66, 141.44, 148.53, 168.58, 171.91.

Compound 9(4-Amino-2-(2-thienyl)benzoyl)-Met-OCH<sub>3</sub>

3820 The title compound can be prepared according to the method used to prepare Compound 8, only substituting thiophene-2-boronic acid for phenyl boronic acid.

Compound 10(4-Amino-2-(1-naphthyl)benzoyl)-Met-OCH<sub>3</sub>

3825 The title compound can be prepared according to the method used to prepare Compound 8, only substituting 1-naphthylboronic acid for phenylboronic acid.

Compound 114-Amino-3'-methylbiphenyl

3830 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Compound 124-Amino-4'-biphenyl carboxylic acid

3835

Step A4-Nitro-4'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-4-methylbenzene.

3840

Step B4-Nitro-4'-biphenyl carboxylic acid

The title compound was prepared by KMnO<sub>4</sub> oxidation of 4-nitro-4'-methylbiphenyl.

3845

Step C4-Amino-4'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-4'-biphenyl carboxylic acid.

3850

Compound 134-Amino-3'-biphenyl carboxylic acidStep A



4-Nitro-3'-methylbiphenyl

3855 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Step B4-Nitro-3'-biphenyl carboxylic acid

3860 The title compound was prepared by  $\text{KMnO}_4$  oxidation of 4-nitro-3'-methylbiphenyl.

Step C4-Amino-3'-biphenyl carboxylic acid

3865 The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-3'-biphenyl carboxylic acid.

Compound 144-Amino-2-methoxy-3'-biphenyl carboxylic acid

3870

Step A2-Methoxy-4-nitro-3'-methylbiphenyl

The title compound was prepared by reaction of 1-bromo-2-methoxy-4-nitrobenzene with 3-methylphenylboronic acid in the presence of palladium acetate.

3875

Step B2-Methoxy-4-nitro-3'-biphenylcarboxylic acid

The title compound was prepared by  $\text{KMnO}_4$  oxidation of 2-methoxy-4-nitro-3'-methylbiphenyl.

3880

Step C4-Amino-2-methoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 2-methoxy-4-nitro-3'-biphenyl carboxylic acid.

3885

Compound 154-Amino-2-isopropyloxy-3'-biphenyl carboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3890

Compound 16

4-Amino-2-phenyl-3'-biphenylcarboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3895

Compound 17(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH<sub>3</sub>Step A2-Bromo-4-nitrobenzoic acid

3900 2-Bromo-4-nitrotoluene (5.0 g, 23.14 mmol) was dissolved in pyridine (23 mL) and water (46 mL). The heterogeneous mixture was heated to 60°C and KMnO<sub>4</sub> (18.29 g, 115.7 mmol) was added carefully. The mixture was then heated under reflux overnight. The reaction mixture was filtered and washed with boiling water. The solution was then made acidic and extracted into ethyl acetate, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed in  
3905 vacuo. The crude product was dissolved in aqueous NaOH and washed with hexanes. The aqueous phase was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solutions were combined and dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed in vacuo to provide the desired product (3.72 g): m.p. 158-160°C; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.81 (1H, d, J=8.5 Hz), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, s); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ  
3910 121.96, 122.75, 129.36, 132.24, 139.52, 149.54, 167.75; Anal. Calc. for C<sub>7</sub>H<sub>4</sub>BrNO<sub>4</sub> •0.1 ethyl acetate, C: 34.88, H: 1.90, N: 5.50; Found, C: 34.68, H: 1.86, N: 5.82.

Step B3,5-Dimethylphenylboronic acid

3915 Magnesium turnings (1.44 g, 59.43 mmol) were covered with dry THF (18.8 mL) in a dried, nitrogen filled flask fitted with an addition funnel and reflux condenser. To this was added 5-bromo-m-xylene (10 g, 54.03 mmol) in THF (15 mL) after initiation of the Grignard reaction. The addition was carried out over several minutes and the reaction mixture was heated at reflux for 1-2 hours until most of the magnesium had reacted. The  
3920 reaction mixture was then cooled and transferred to an addition funnel fitted to a nitrogen filled flask containing triisopropyl borate (24.9 mL) at -70°C. The dropwise addition was carried out over several minutes and the mixture warmed to room temperature and stirred overnight. The grey solution was poured onto 2 M HCl and immediately turned yellow. The solution was extracted with Et<sub>2</sub>O and the Et<sub>2</sub>O fractions were combined, dried over  
3925 MgSO<sub>4</sub> and the solvent was removed in vacuo to provide the desired product (2.41 g): m.p. 249-251°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.44 (6H, s), 7.23 (1H, s), 7.84 (2H, s); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 21.36, 133.28, 134.39, 137.48.

Step C3930 4-Nitro-2-(3,5-dimethylphenyl)benzoic acid

2-Bromo-4-nitrobenzoic acid (0.43 g, 2.03 mmol) and 3,5-dimethylphenyl boronic acid (0.334 g, 2.23 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added  $\text{Cs}_2\text{CO}_3$  (1.66 g, 5.08 mmol) followed by  $\text{Pd}(\text{Ph}_3\text{P})_4$  (0.12 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and  
3935 extracted with  $\text{Et}_2\text{O}$ . It was dried over  $\text{MgSO}_4$  and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using a 9:1 mixture of hexanes and ethyl acetate to provide the desired product (0.34 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.36 (6H, s), 6.99 (2H, s), 7.07 (1H, s), 8.03 (1H, d,  $J=9.0$  Hz), 8.23-8.25 (2H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.28, 121.68, 123.68, 125.74, 126.07, 130.22, 131.19, 131.31, 135.04, 138.21,  
3940 144.74, 170.75.

Step D(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH<sub>3</sub>

4-Nitro-2-(3,5-dimethylphenyl)benzoic acid (0.15 g, 0.55 mmol), methionine methyl ester  
3945 hydrochloride (0.11 g, 0.55 mmol), EDCI (0.11 g, 0.55 mmol), HOBT (0.07 g, 0.55 mmol) and triethylamine (0.08 mL) in dry methylene chloride (2.2 mL) were reacted and worked up according to the procedure for (N-BOC-4-aminobenzoyl)-Met-OCH<sub>3</sub> as described above. After recrystallization from ethyl acetate and hexanes, the desired product was obtained (0.13 g): m.p. 122-124°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.2-1.84 (1H, m), 1.85-  
3950 1.97 (1H, m), 2.01 (3H, s), 2.05 (3H, t,  $J=7.7$  Hz), 2.38 (6H, s), 3.70 (3H, s), 4.67-4.74 (1H, m), 6.03 (1H, d,  $J=7.9$  Hz), 7.05 (2H, s), 7.09 (1H, s), 7.84-7.87 (1H, m), 7.84-7.87 (1H, m) 8.23-8.26 (2H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.20, 21.26, 29.22, 31.15, 51.79, 52.57, 122.07, 125.11, 126.27, 130.03, 130.53, 137.77, 138.82, 140.29, 141.56, 148.41, 167.14, 171.53.

3955

Step E(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH<sub>3</sub>

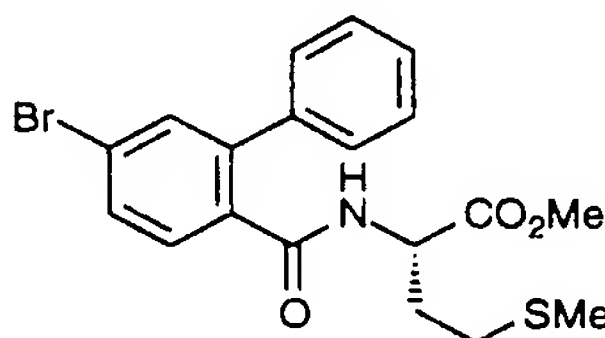
(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH<sub>3</sub> (0.11 g, 0.26 mmol) was dissolved in ethyl acetate (3.0 mL). To this mixture was added  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (0.3 g, 1.30 mmol) and  
3960 the reaction was heated under nitrogen at reflux for 6 hours. The mixture was worked up as described above for (4-amino-2-phenylbenzoyl)-Met-OCH<sub>3</sub> to give the desired product (0.15 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 1.99 (3H, s), 2.05 (2H, t,  $J=7.6$  Hz), 2.33 (6H, s), 3.64 (3H, s), 3.93 (2H, br s), 4.61-4.64 (1H, m), 5.82 (1H, d,  $J=7.7$  Hz), 6.49 (1H, d,  $J=2.3$  Hz) 6.62 (1H, dd,  $J=8.4, 2.4$  Hz), 6.98 (2H, s),

3965 7.00 (1H, s), 7.65 (1H, d,  $J=8.3$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.08, 21.17, 29.28, 31.49, 51.70, 52.18, 113.30, 115.94, 123.55, 126.36, 129.32, 131.23, 138.15, 140.72, 141.92, 148.40, 168.45, 172.01.

#### Preparation 1

3970 Anilines of the formula B-NH<sub>2</sub>

The anilines from Table 1, entries 10-126 (B-NH<sub>2</sub>) are prepared using the procedures for Compounds 1-18 with the exception that methionine methyl ester is replaced by methioninesulfone methyl ester, (S-Me)cysteine methyl ester, serine methyl ester, (O-Me)serine methyl ester, (O-Me)homoserine methyl ester, homoserine lactone, isoleucine methyl ester, leucine methyl ester, norleucine methyl ester, norvaline methyl ester, cyclohexylalanine methyl ester, phenylalanine methyl ester, or glutamic acid dimethyl ester.



3980

#### Preparation 2

##### 4-Bromo-2-phenylbenzoyl methionine methyl ester

#### Preparation 2A

##### 4-Bromo-2-phenylbenzoic acid methyl ester

3985 A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous HBr is treated with  $\text{NaNO}_2$  (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

3990

#### Preparation 2B

##### 4-Bromo-2-phenylbenzoic acid

3995 To a solution of the resultant compound from Preparation 2A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Preparation 2C4000      4-Bromo-2-phenylbenzoyl methionine methyl ester

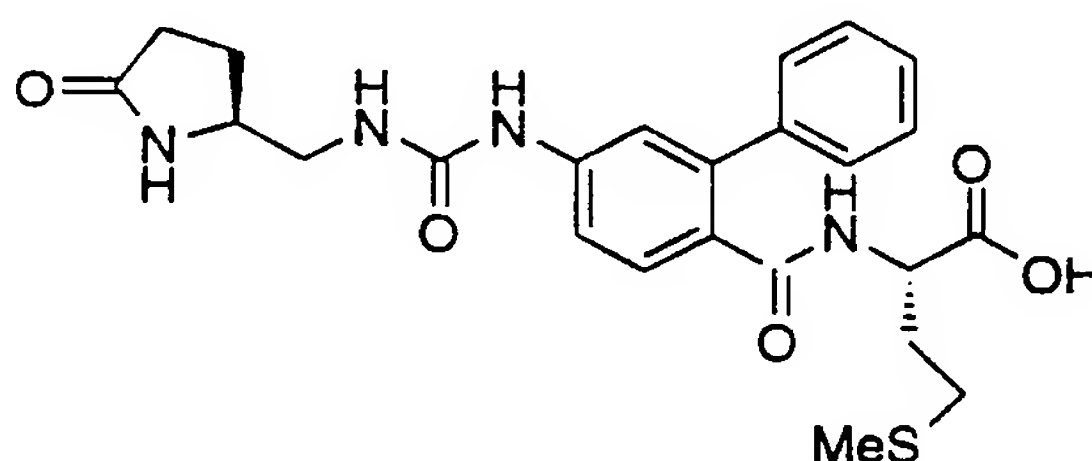
To a solution of the resultant compound from Preparation 2B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged  
 4005 complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Preparation 2D4010      4-Bromo-2-phenylbenzoyl methionine methyl ester alternate procedure

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous HBr is treated with NaNO<sub>2</sub> (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC  
 4015 analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 3Arylbromides of the formula B-Br

The anilines from Table 1 (B-NH<sub>2</sub>) are reacted according to the procedures of Preparation 2  
 4020 to provide the arylbromides listed in Table 2.

Example 14025      4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionineExample 1AMethyl 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoate



To a solution of methyl 4-amino-2-phenylbenzoate hydrochloride (1.0 equivalent) in  
4030 toluene is added triphosgene (0.33 equivalent) and the mixture is heated at reflux until  
judged complete by TLC analysis. The intermediate is reacted without further  
purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine  
(2.0 equivalents). When judged complete by TLC analysis, the reaction is taken up in  
ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by  
4035 chromatography on silica gel.

#### Example 1B

##### 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoic acid

To a solution of the resultant compound from Example 1A (1.0 equivalent) in a 3:1  
4040 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of  
LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated  
and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate  
which is dried and evaporated prior to purification by chromatography on silica gel.

#### Example 1C

##### 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 1B (1.0 equivalent) in  
dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5  
4050 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-  
dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When  
judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is  
washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude  
reaction mixture is purified by column chromatography to afford the title product.

4055

#### Example 1D

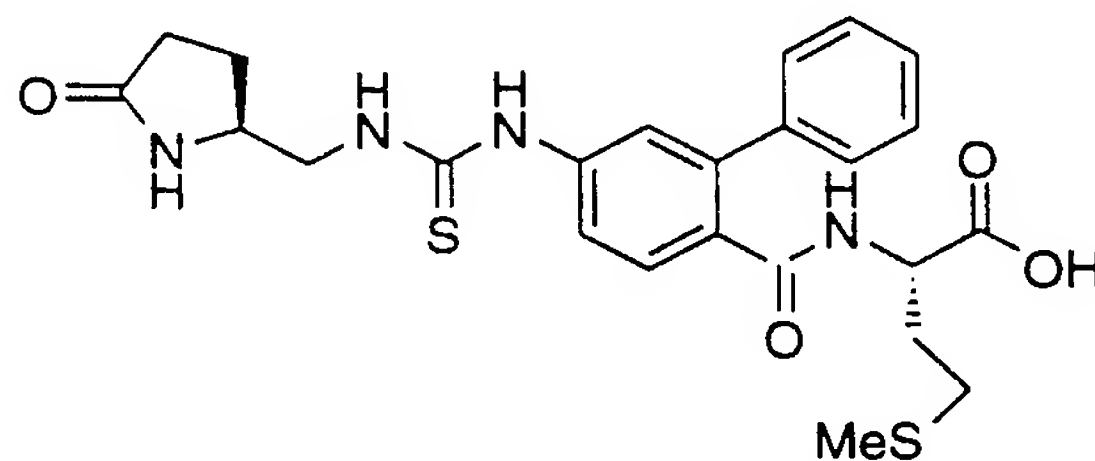
##### 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in  
4060 methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and  
triethylamine (2.0 equivalents). The intermediate is reacted without further purification  
with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0  
equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl  
acetate and washed with 1N HCl and brine, evaporated, and purified by  
4065 chromatography on silica gel.

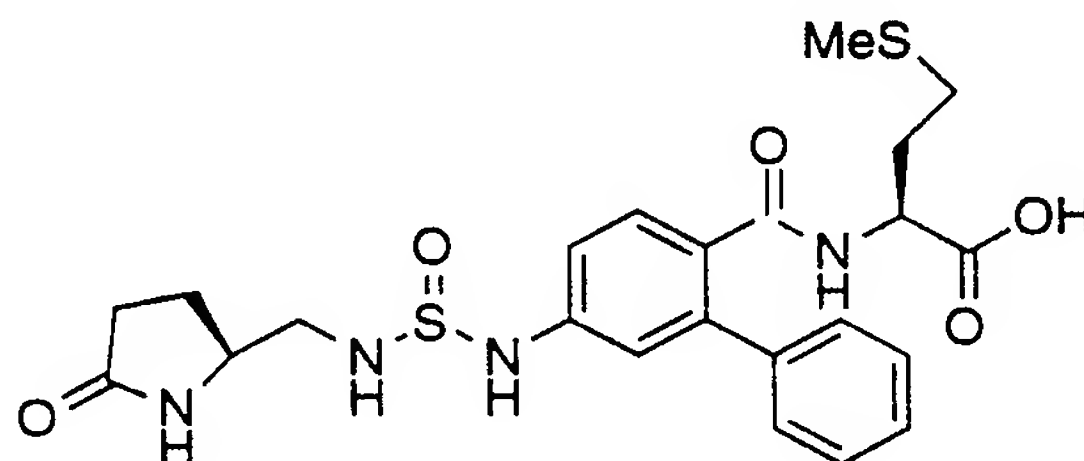
#### Example 1E

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 1C in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 24-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 34-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionineExample 3A4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine methyl ester

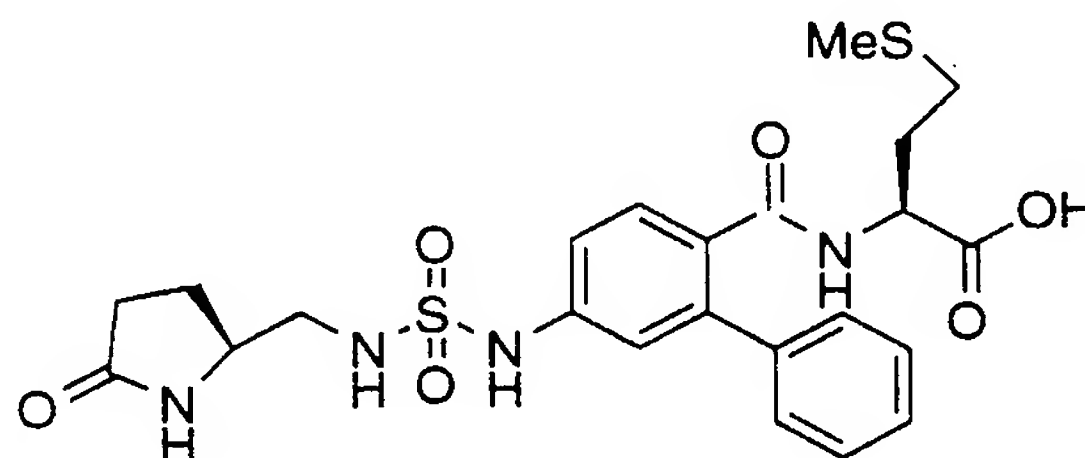
To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added thionyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 3B

4095 4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 3A in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

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Example 4

4105 4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine

Example 4A

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

4110 To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added sulfonyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

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Example 4B

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate procedure

4120 A solution of 1 equivalent of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and sulfonyl chloride (1.0 equivalent) in acetonitrile with a catalytic amount of antimony(V) chloride is heated to reflux until judged complete by TLC analysis. The solution is then cooled, filtered, and all volatiles are removed under reduced pressure. The residue is taken up in dichloromethane and treated with triethylamine (1 equivalent and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent). When the reaction is judged complete by



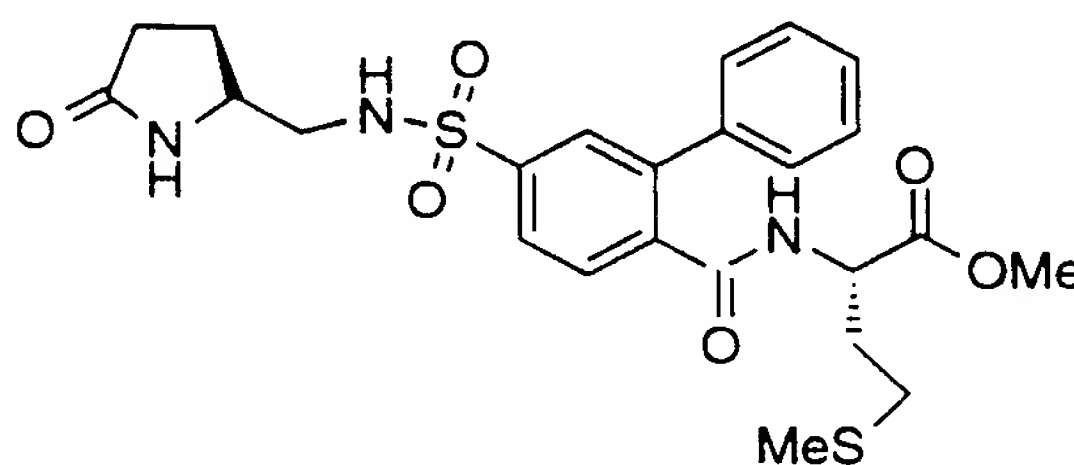
4125 TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

#### Example 4C

#### 4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

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The resultant compound from Example 4A is hydrolyzed according to the procedure of Example 1B to give the title product.



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#### Example 5

#### 4-((S)-2-Pyrrolidone-5-methylaminosulfonyl)-2-phenylbenzoyl methionine

#### Example 5A

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#### 4-Chlorosulfonyl-2-phenylbenzoic acid methyl ester

To a solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists. The chlorodiazonium salt is poured into a solution of sulfur dioxide (10 equivalents), copper (II) chloride (0.5 equivalent) and KCl (1.1 equivalents) in dioxane. When TLC analysis indicated that the reaction is complete, the mixture is diluted with water and extracted into benzene which is dried and evaporated to give the title sulfonyl chloride

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#### Example 5B

#### 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid methyl ester

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To a solution of the resultant compound from Example 5A (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

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#### Example 5C

#### 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 5B is hydrolyzed according to the procedure of Example 1B to give the title product.

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Example 5D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoyl methionine methyl ester

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To a solution of the resultant compound from Example 5C (1.0 equivalent) in (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

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Example 5E4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

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To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists at which time the chlorodiazonium salt will be treated with gaseous sulfur dioxide and copper (II) chloride to give the sulfonyl chloride (0.1 equivalent). This intermediate is reacted with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) according to the procedure of Example 5B to give the title compound.

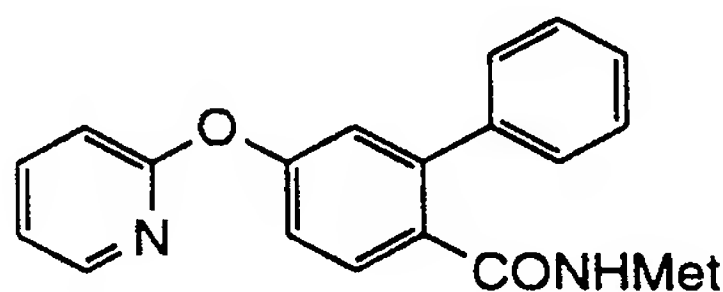
4180

Example 5F4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

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To a solution of the resultant compound from Example 5D (1.0 equivalent) in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

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Example 64-(2-pyridyloxy)-2-phenylbenzoylmethionineExample 6A4195 4-Hydroxy-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous H<sub>2</sub>SO<sub>4</sub> is treated with NaNO<sub>2</sub> (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 6B4-(2-Pyridyloxy)-2-phenylbenzoic acid methyl ester

A solution of the resultant phenol from Example 6A (1.0 equivalent) is treated with 2-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K<sub>2</sub>CO<sub>3</sub> (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6C4210 4-(2-Pyridyloxy)-2-phenylbenzoic acid

A solution of the resultant ester from Example 6B (1.0 equivalent) in aqueous methanol is treated with NaOH (2.0 equivalents) and stirred until the reaction is deemed complete by TLC analysis. The mixture is acidified, diluted with water, and extracted into ethyl acetate which is dried and evaporated. Chromatography on silica gel provides the title product.

Example 6D4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 6C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 6E4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester, alternate procedure

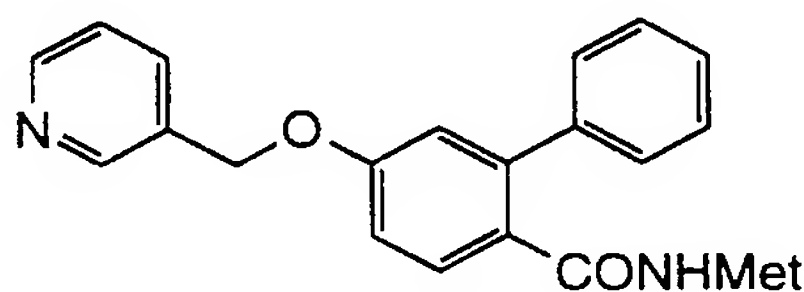
A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H<sub>2</sub>SO<sub>4</sub> is treated with NaNO<sub>2</sub> (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated to form the phenol which is purified by chromatography on silica gel. A solution of this phenol (1.0 equivalent) is treated with 3-bromopyridine (1.0 equivalent) in the presence of a

NaH (1.0 equivalent), or  $K_2CO_3$  (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

#### Example 6F

##### 4-(2-pyridyloxy)-2-phenylbenzoylmethionine

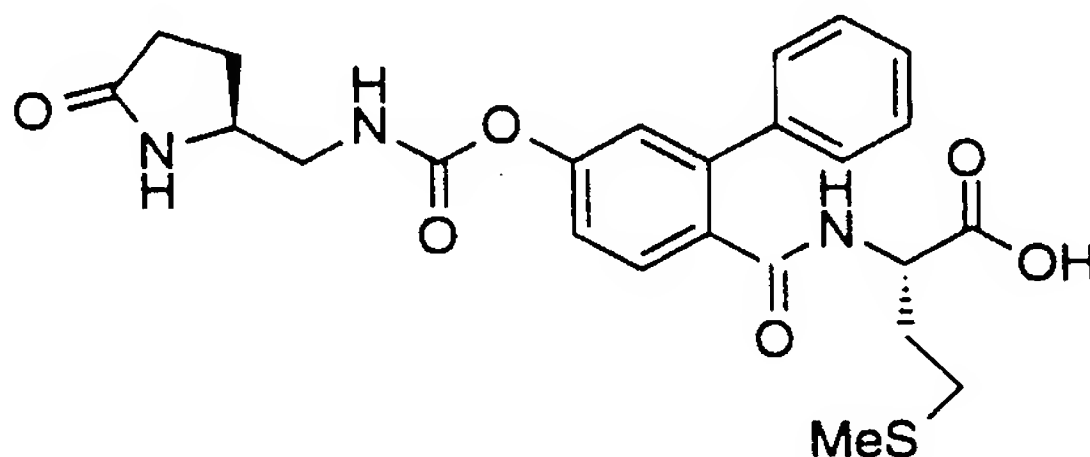
The resultant compound from Example 6E is hydrolyzed according to the procedure of Example 1B to give the title compound.



#### Example 7

##### 4-(3-pyridylmethylenoxy)-2-phenylbenzoylmethionine

The title compound is prepared as described in Example 6 with the exception that 2-bromopyridine is replaced by 3-chloromethylpyridine hydrochloride.



#### Example 8

##### 4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

#### Example 8A

##### 4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine methyl ester

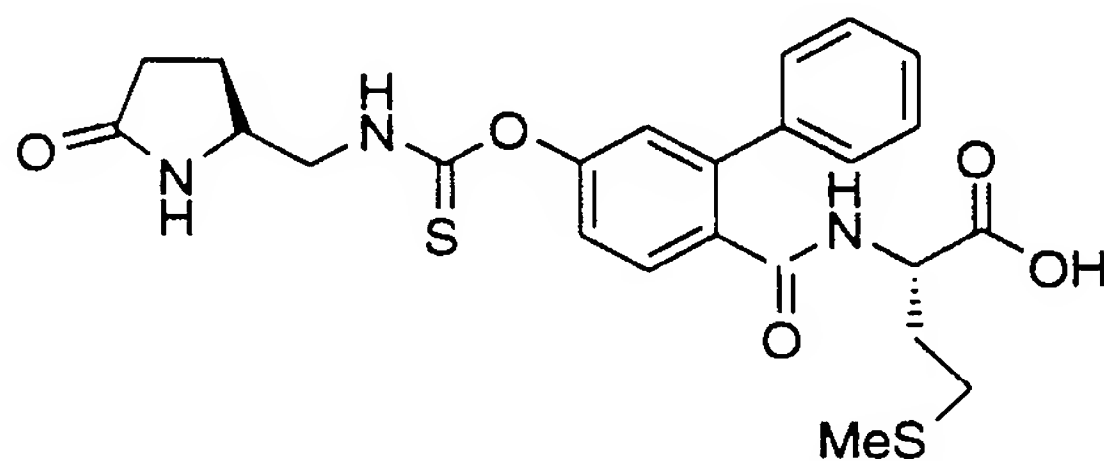
To a solution of 4-hydroxy-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) from Example 6E in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The chloroformate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone

(1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

#### Example 8B

##### 4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

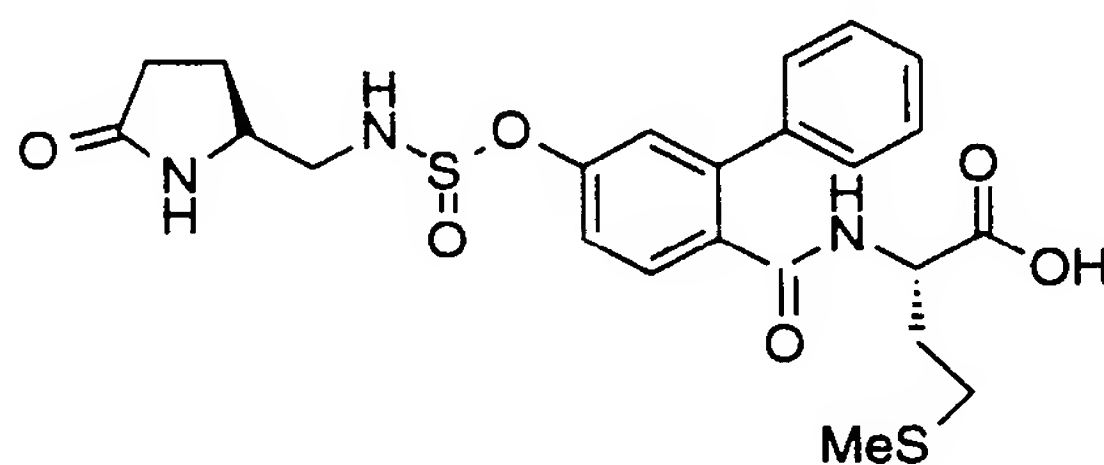
The resultant compound from Example 8A is hydrolyzed according to the procedure of Example 1B to give the title product.



#### Example 9

##### 4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxy-2-phenylbenzoyl methionine methyl ester

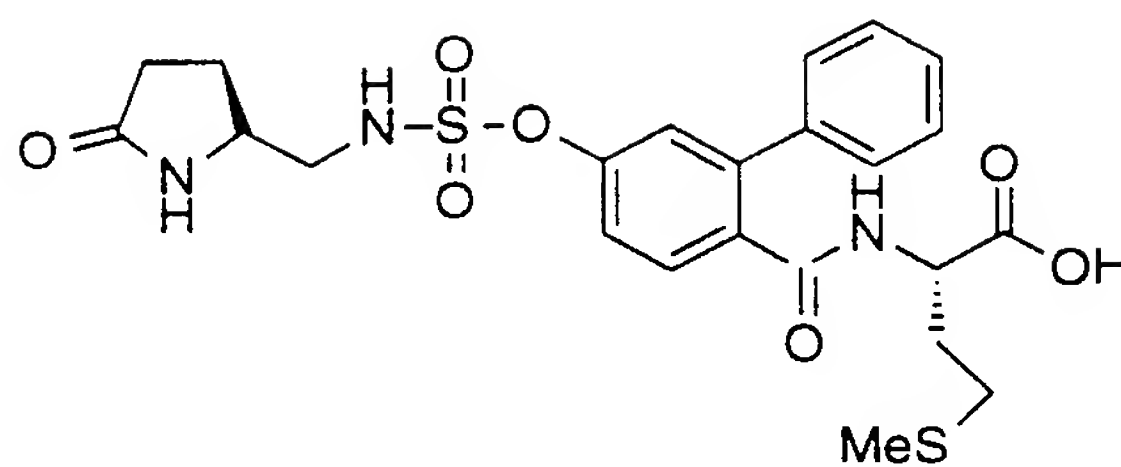
The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thiophosgene.



#### Example 10

##### 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfinyloxy-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride.

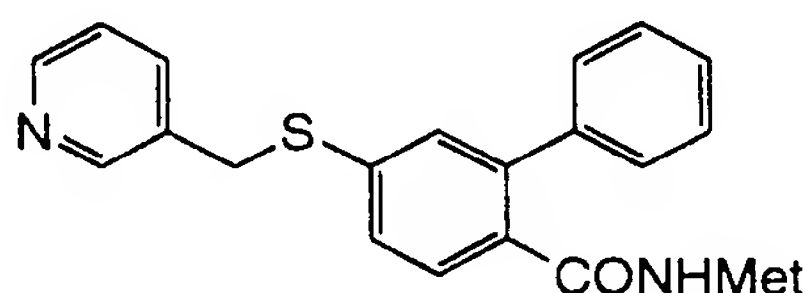


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Example 114-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy)-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride.

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Example 124-(3-Pyridylmethylthio)-2-phenylbenzoylmethionineExample 12A4-Mercapto-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous  $\text{H}_2\text{SO}_4$  is treated with  $\text{NaNO}_2$  (1.1 equivalents) to form the diazonium salt. The reaction is treated with  $\text{S}_8$  (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel.

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Example 12B4-(2-Pyridylmethylthio)-2-phenylbenzoic acid methyl ester

A solution of the resultant thiophenol (1.0 equivalent) from Example 12A is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a  $\text{NaH}$  (2.0 equivalents), or  $\text{K}_2\text{CO}_3$  (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

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Example 12C4-(2-Pyridylthiomethylen)-2-phenylbenzoic acid

The resultant compound from Example 12B is hydrolyzed according to the procedure of Example 6C to give the title acid.

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Example 12D4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 12C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

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Example 12E4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 1

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A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous  $\text{H}_2\text{SO}_4$  is treated with  $\text{NaNO}_2$  (1.1 equivalents) to form the diazonium salt. The reaction is treated with  $\text{S}_8$  (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. The thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a  $\text{NaH}$  (2.0 equivalents), or  $\text{K}_2\text{CO}_3$  (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

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Example 12F4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 2

Methyl 4-amino-2-phenylbenzoate (100 mmol) is mixed in 50% sulfuric acid, and is cooled by a ice-water bath. To the above mixture with good stirring is added slowly a cold solution of sodium nitrite (110 mmol) in water, the reaction temperature is kept under 10 °C.

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Powdered anhydrous sodium carbonate (100 mmol) is carefully added to the cold reaction mixture in small portions, until the reaction mixture reaches pH 7 to 8. Then, the reaction mixture is added in small portions to a solution of sodium p-methoxybenzylsulfide (prepared from reaction 110 mmol of p-methoxybenzylthiol with 55 mmol of 2.0 M  $\text{NaOH}$  aqueous solution). After completion of the addition, the reaction mixture is refluxed until

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judged complete by TLC analysis. The reaction mixture is then extracted with ether, and the organic extracts are washed sequentially with aqueous sodium carbonate solution, water and



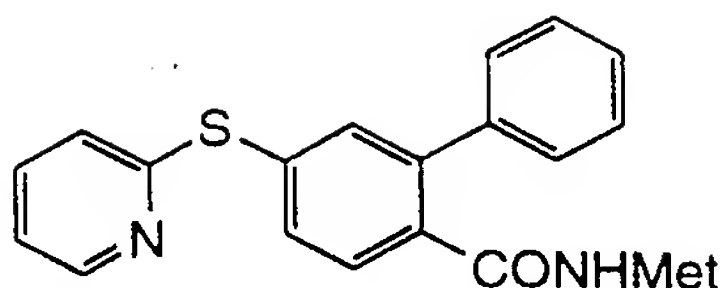
brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The product thus obtained is dissolved in methanol and water, followed by addition of lithium hydroxide (200 mmol),  
4355 and the mixture is refluxed until hydrolysis is judged complete by TLC analysis. The reaction mixture is then acidified with 6 N HCl, and extracted into ethyl acetate. The organic extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product obtained is redissolved in methylene chloride, followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.1 equivalent)  
4360 and 1-hydroxybenzotriazole (1.2 equivalent). The reaction is stirred until it is judged complete by TLC analysis, and then is diluted with ether. The mixture is washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The resulting product is dissolved in trifluoroacetic acid and anisole (1.5 equivalent), and mercury diacetate (1.2  
4365 equivalent) is added. After TLC shows no starting material left, the reaction mixture is diluted with ether, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material is purified by column chromatography to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0  
4370 equivalent) in the presence of a NaH (2.0 equivalents), or K<sub>2</sub>CO<sub>3</sub> (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

#### Example 12G

##### 4375 4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The resultant compound from Example 12D is hydrolyzed according to the procedure of Example 1B to give the title product.





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Example 134-(2-Pyridylthio)-2-phenylbenzoylmethionine

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Example 13A4-Fluoro-2-phenyl benzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous  $\text{HBF}_4$  is treated with  $\text{NaNO}_2$  (1.1 equivalents) until an excess of nitrous acid persists. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by

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chromatography on silica gel.

Example 13B4-Fluoro-2-phenyl benzoic acid

The resultant compound from Example 13A is hydrolyzed according to the procedure of Example 6C to give the title acid.

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Example 13C4-Fluoro-2-phenyl benzoyl methionine methyl ester

The resultant product from Example 13B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

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Example 13D4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester

A mixture of the resultant fluorobenzoate from Example 13C (1.0 equivalent) and 2-mercaptopyridine (1.0 equivalent) is treated with  $\text{K}_2\text{CO}_3$  (2.0 equivalents) or  $\text{NaH}$  (1.0 equivalent) in DMF or DMSO and is stirred until the reaction is judged complete by TLC analysis. The mixture is diluted with water and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

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Example 13E4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous  $\text{H}_2\text{SO}_4$  is treated with  $\text{NaNO}_2$  (1.1 equivalents) to form the diazonium salt. The

reaction is treated with S<sub>8</sub> (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalent), or K<sub>2</sub>CO<sub>3</sub> (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

#### Example 13F

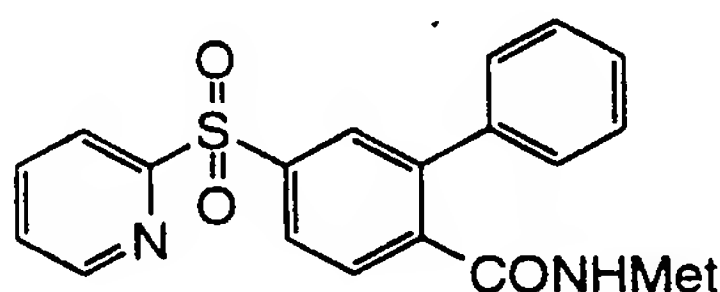
##### 4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 2

A solution of the resultant thiophenol from Example 12A (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K<sub>2</sub>CO<sub>3</sub> (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel. The resultant ester is hydrolyzed according to the procedure of Example 6C and then is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

#### Example 13G

##### 4-(2-Pyridylthio)-2-phenylbenzoylmethionine

The resultant compound from Example 13D is hydrolyzed according to the procedure of Example 1B to give the title product.



#### Example 14

##### 4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

#### Example 14A

##### 4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid methyl ester

A solution of 4-(2-pyridylthio)-2-phenylbenzoic acid methyl ester (Example 13F) is carefully treated with two equivalents of *meta*-chloroperbenzoic acid in methylene chloride at low temperature and the reaction is then quenched with aqueous Na<sub>2</sub>SO<sub>3</sub> when judged complete by TLC analysis. The layers are separated and the organic phase is extracted with

aqueous NaHCO<sub>3</sub> to remove the *m*-chlorobenzoic acid. The product is isolated by removal of the solvent and is purified by chromatography on silica gel.

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Example 14B4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 14A is hydrolyzed according to the procedure of Example 6C to give the title acid.

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Example 14C4-(2-pyridylsulfonyl)-2-phenylbenzoylmethionine methyl ester

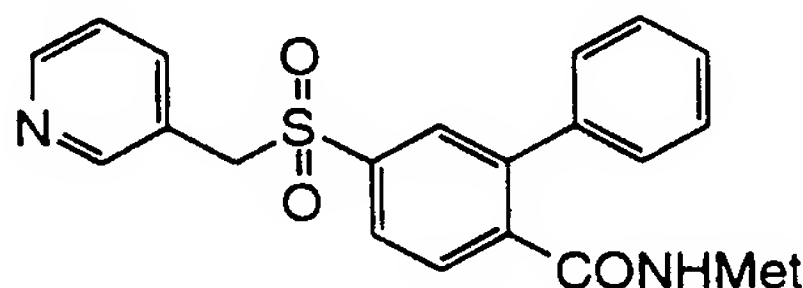
The resultant product from Example 14B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

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Example 14D4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

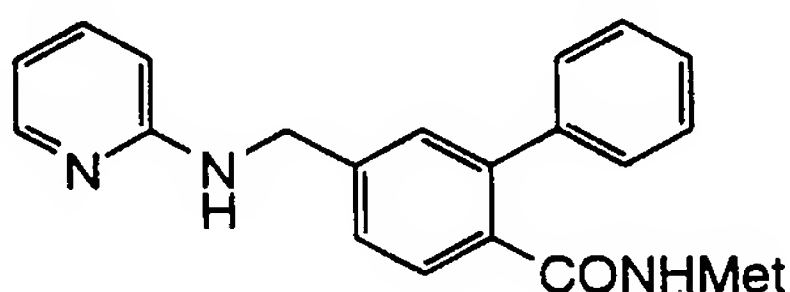
The resultant compound from Example 14C is hydrolyzed according to the procedure of Example 1B to give the title product.

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Example 154-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

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The title compound is prepared from the resultant product of Example 12B using the procedures from Example 14.



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Example 164-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

Example 16A4480                    2-Phenylterephthalic acid mono methyl ester

A solution of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), Pd(OAc)<sub>2</sub> (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16B4-(Hydroxymethyl)-2-phenylbenzoic acid methyl ester

The resultant acid from Example 16A (1.0 equivalent) is treated with a slight excess of N-methylmorpholine (1.1 equivalent) and isobutylchloroformate (1.0 equivalent) in THF at 0° C. The mixture is then treated with NaBH<sub>4</sub> (1.0 equivalent) and aqueous NaHCO<sub>3</sub> and stirred at 0° C until the reaction is judged complete by TLC analysis. The mixture is poured into dilute aqueous acid and extracted into ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16C4-(Hydroxymethyl)-2-phenylbenzoic acid

The resultant compound from Example 16B is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 16D4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester

The resultant product from Example 16C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 16E4-formyl-2-phenylbenzoyl methionine methyl ester

A mixture of the resultant alcohol from Example 16D (1.0 equivalent), N-methylmorpholine-N-oxide (1.5 equivalents), molecular sieves, and a catalytic amount of TPAP is stirred in a CH<sub>2</sub>Cl<sub>2</sub>/acetonitrile mixture until the reaction is judged complete by TLC analysis. The mixture is diluted with ethyl ether and filtered through SiO<sub>2</sub>. The product is purified by chromatography on silica gel.

Example 16F4-(formyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

A mixture of (2-phenyl-4-bromobenzoyl) methionine methyl ester (100 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (100 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mmol) in toluene and 2 M sodium carbonate in water (100 mL) is heated at 80 °C until the starting methyl ester disappears. The resulting mixture is extracted with ether, and washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. To a solution of the resulting vinyl compound in dioxane/water (4/1) is added osmium tetraoxide (0.03 equivalent), N-methylmorpholine N-oxide (3 equivalents), and the reaction is stirred at 25 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16G4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

To a solution of the resultant compound from Example 16E in ethanol at 0 °C is added sodium borohydride (0.5 equivalent), and the reaction is stirred at 0 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

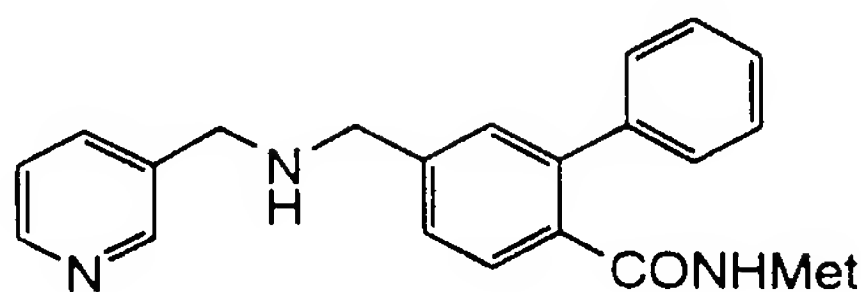
Example 16H4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant aldehyde from Example 16E (1.0 equivalent), 2-aminopyridine (1.0 equivalent) and NaCNBH<sub>3</sub> (1.5 equivalents) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO<sub>3</sub> and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 16I4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

The resultant compound from Example 16H is hydrolyzed according to the procedure of Example 1B to give the title product.

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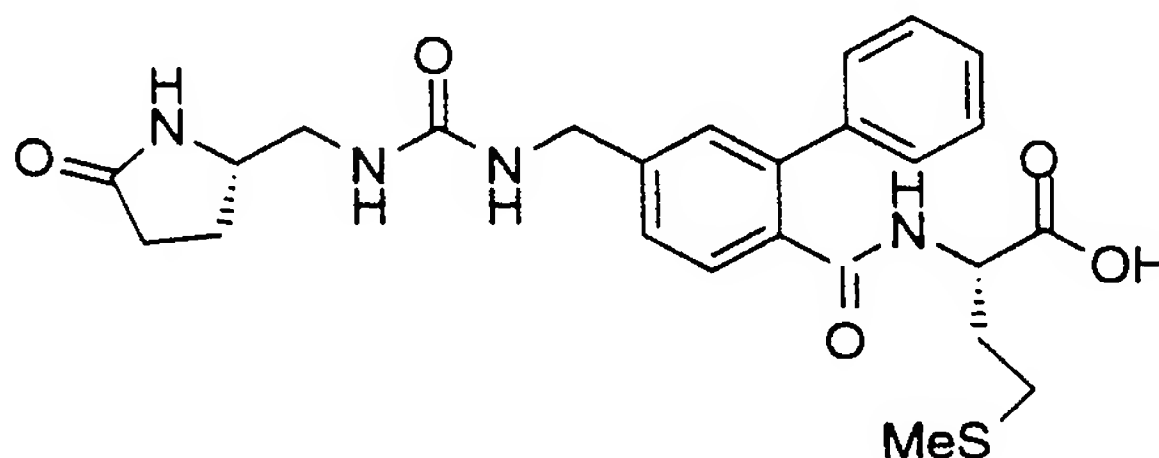


#### Example 17

4560

#### 4-[(3-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 16F-G and replacing 2-aminopyridine with 3-aminomethylpyridine affords the title product.



4565

#### Example 18

#### 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

4570

#### Example 18A

#### 4-(Azidomethyl)-2-phenylbenzoyl methionine methyl ester

To triphenylphosphine (1.0 equivalent) in tetrahydrofuran (THF) at  $-78^{\circ}\text{C}$  is added diethyl azodicarboxylate (1.0 equivalent) in THF. To this mixture is added a solution of hydrazoic acid in benzene (2.0 equivalents) and then the resultant compound from Example 16D (1.0 equivalent). After one hour the mixture was warmed to room temperature, stirred until the reaction is judged complete by TLC analysis, evaporated and chromatographed on silica gel to afford the title product.

4575

#### Example 18B

4580

#### 4-(Aminomethyl)-2-phenylbenzoyl methionine methyl ester

To the resultant compound from Example 18A in methanol is added triethylamine (3.0 equivalent) and propane 1,3-dithiol (3.0 equivalents). After the reaction is judged complete

by TLC analysis, the mixture is filtered and evaporated. Chromatography of the residue on silica gel provides the title product.

4585

#### Example 18C

##### 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 18B (1.0 equivalent) in methylene chloride is added triphosgene (0.33 equivalent) and triethyl amine (2.0 equivalents). This intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

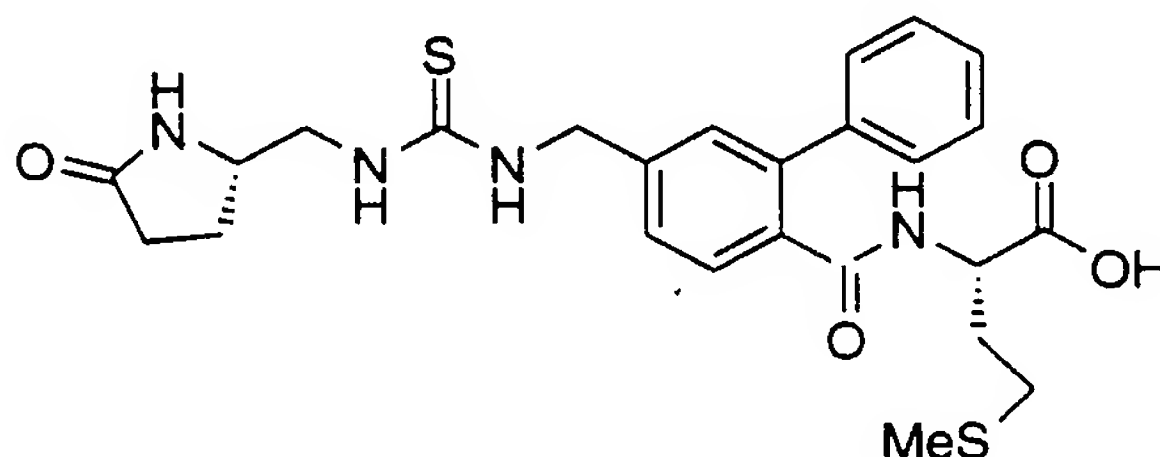
4595

#### Example 18D

##### 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

The resultant compound from Example 18C is hydrolyzed according to the procedure of Example 1B to give the title product.

4600

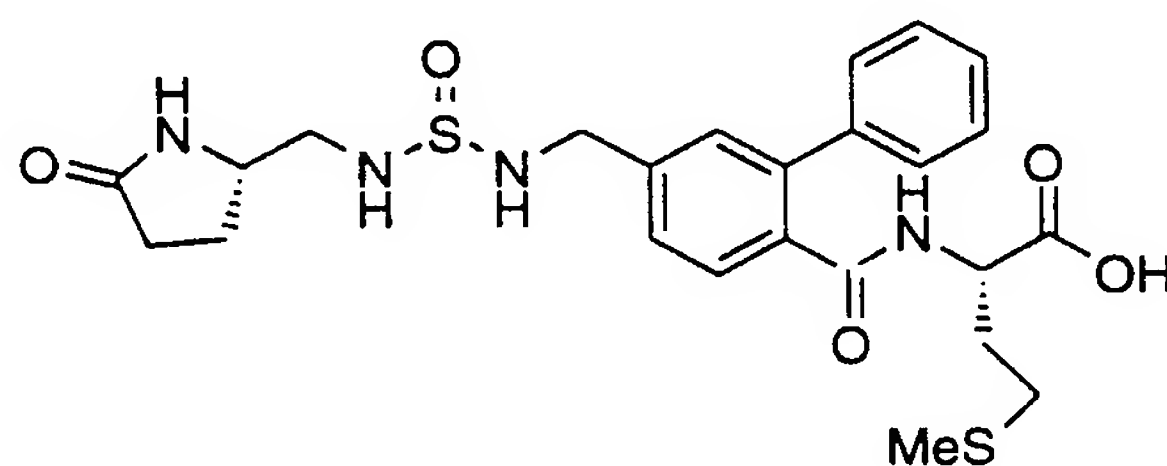


#### Example 19

##### 4-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

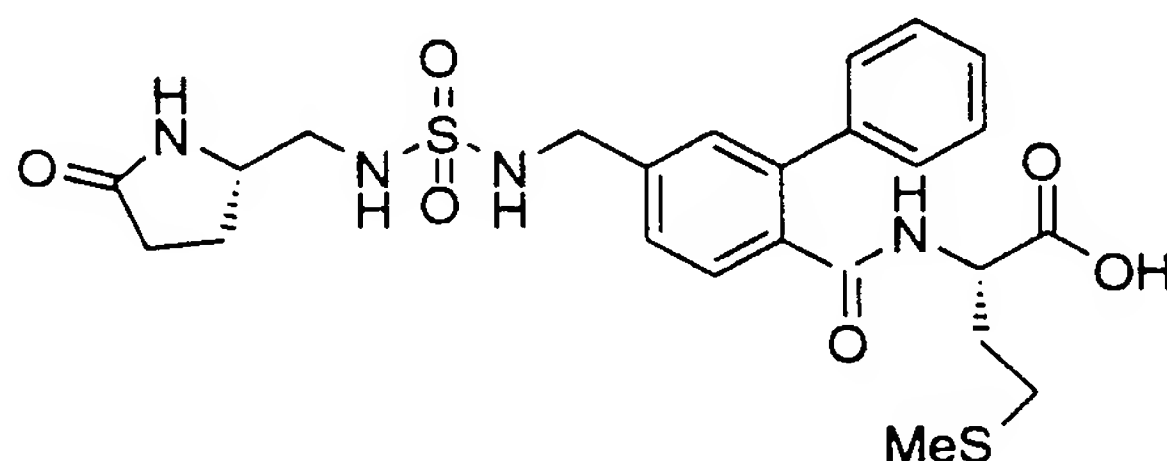
4610



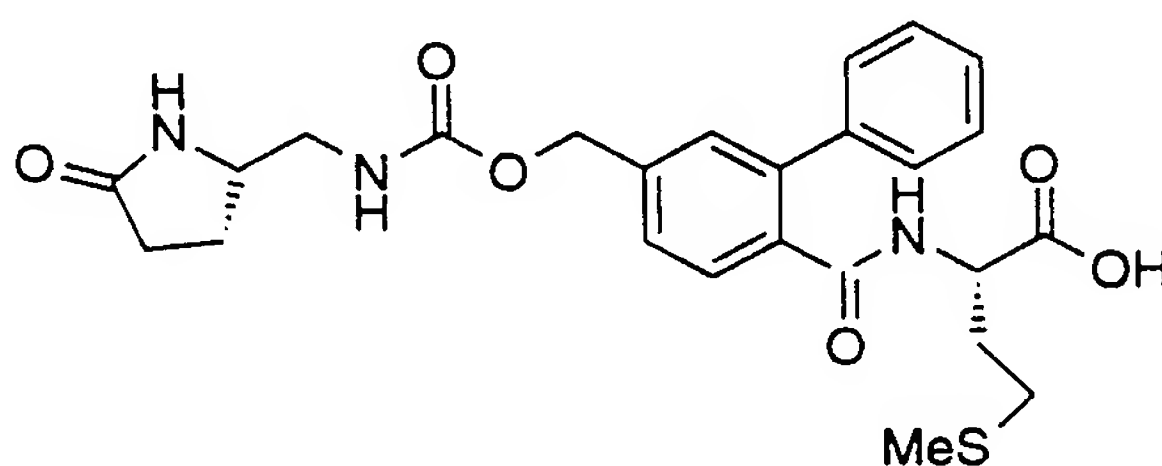


Example 204-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)aminomethyl-2-phenylbenzoyl methionine

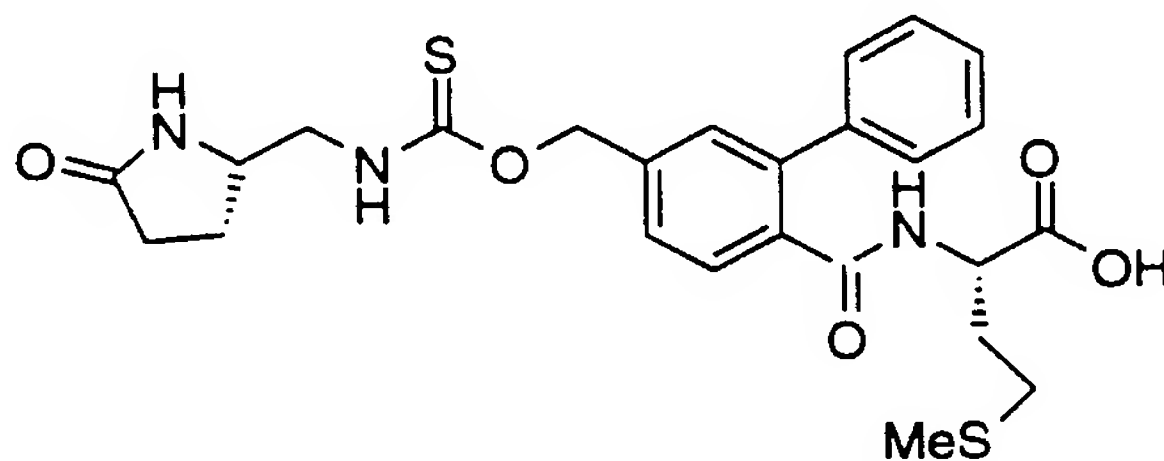
The title compound is prepared as described in Example 18 with the exception that  
4615 triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent).

Example 214-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)aminomethyl-2-phenylbenzoyl methionine

Using the Procedure of Example 4 with the resultant compound from Example 18B affords  
the title product.

Example 224-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxymethylene)-2-phenylbenzoyl methionine

Using the procedure of Example 8 with the resultant compound from Example 16D provides  
the title product.

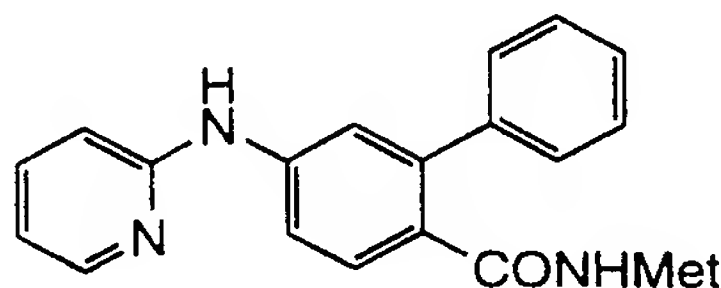
Example 23



4635 4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxymethylene)-2-phenylbenzoyl  
methionine

Using the procedure of Example 8 with the resultant compound from Example 16D and replacing triphosgene (0.33 equivalent) with thiophosgene (1.0 equivalent) provides the title product.

4640



Example 24

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

4645

Example 24A

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine methyl ester

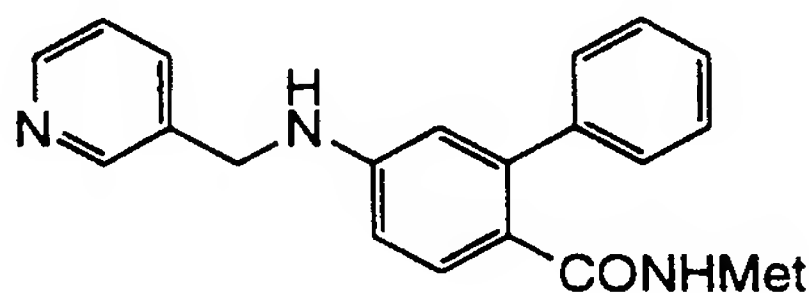
4-Amino-2-phenylbenzoyl methionine (1.0 equivalent) methyl ester and 2-bromopyridine hydrobromide (1.0 equivalent) in pyridine are heated until the reaction is judged complete by  
4650 TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 24B

4655

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 24A is hydrolyzed according to the procedure of Example 1B to give the title product.



4660

Example 25

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

Example 25A

4665

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine methyl ester

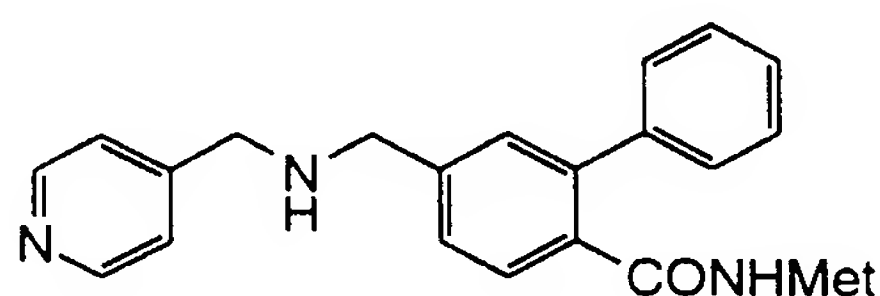
A mixture of 3-pyridinecarboxaldehyde (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and NaCNBH<sub>3</sub> (1.0 equivalent) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO<sub>3</sub> and extracted into ethyl acetate which is dried and evaporated.

4670 Chromatography of the residue on silica gel affords the title compound.

Example 25B

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 25A is hydrolyzed according to the procedure of  
4675 Example 1B to give the title product.



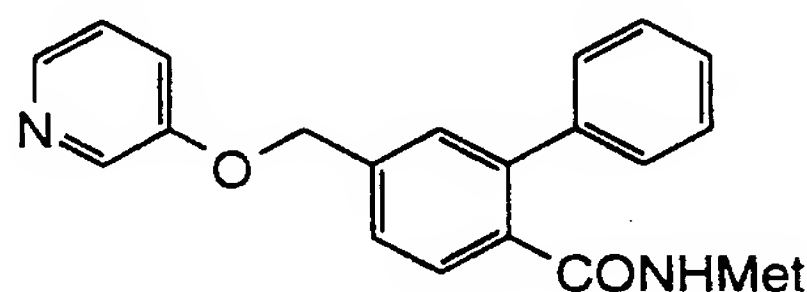
4680

Example 26

4-[(4-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 25 with the resultant amine from Example 18B and 3-pyridinecarboxaldehyde affords the title product.

4685



Example 27

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

4690

Example 27A

4-(p-Toluenesulfonyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 16D (1.0 equivalent) and *p*-toluenesulfonyl chloride (1.0 equivalent) in pyridine are stirred until the reaction is judged complete by TLC analysis.

4695 The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 27B

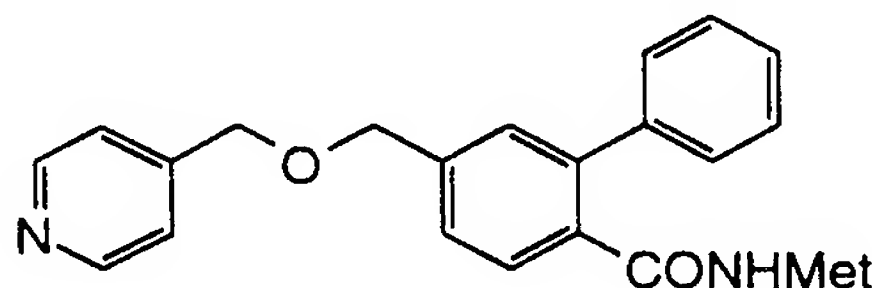
4700 4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine methyl ester

3-Hydroxypyridine (1.0 equivalent) is treated with sodium hydride (1.0 equivalent) in DMSO, then the resultant compound from Example 27A (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by  
4705 chromatography on silica gel.

Example 27C

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

The resultant compound from Example 27B is hydrolyzed according to the procedure of  
4710 Example 1B to give the title product.

Example 28

4715 4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine

Example 28A

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

Using the procedure of Example 27B but replacing 3-hydroxypyridine with 3-  
4720 hydroxymethylpyridine affords the title compound.

Example 28B

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester, alternate  
procedure

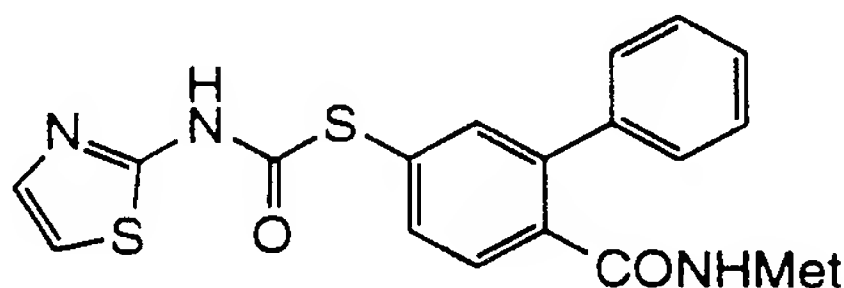
4725 The resultant compound from Example 16D (1.0 equivalent) is treated with sodium hydride (2.0 equivalents) in DMSO, then 3-chloromethylpyridine hydrochloride (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

4730

Example 28C

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 28A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 29{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionineExample 29AThiazol-2-ylisocyanate

A solution of 2-aminothiazol (1.0 mmol), triphosgene (0.34 mmol) and triethylamine (1.0 mmol) in toluene (10 mL) is refluxed until TLC shows no starting amine left. The solvent is then removed in vacuo, and the resulting material is used without further purification.

Example 29B{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester

A solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1.0 mmol) and the isocyanate prepared in example 29A (1.0 mmol) in THF is refluxed until TLC shows no thiol left. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

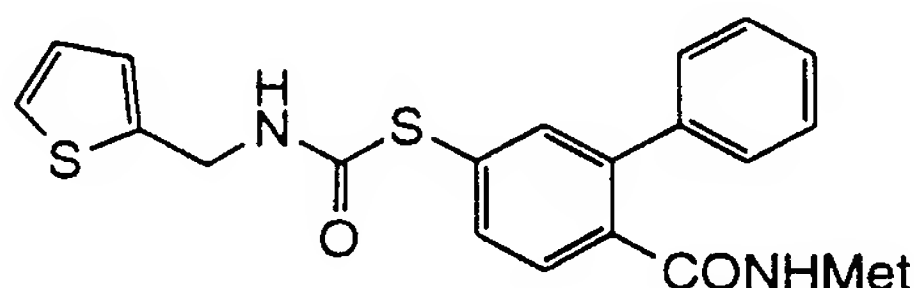
Example 29C{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester, alternate procedure

To a solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The thiochloroformate is reacted without further purification with 2-aminothiazol (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 29D{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

The resultant compound from Example 29B is hydrolyzed according to the procedure of Example 1B to give the title product.

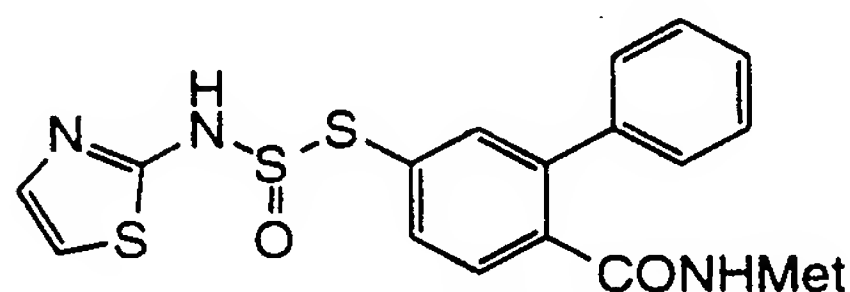
4770

Example 30

4775

{2-Phenyl-4-[(thien-2-ylmethylamino)carbonylthio]benzoyl}-methionine

Using the procedure of Example 29 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



4780

Example 31{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionineExample 31A

4785

(N-Thionyl)thiazol-2-ylamine

A solution of 2-aminothiazol (1.0 mmol), in thionyl chloride is heated at reflux until the reaction is judged to be complete by TLC analysis. Then, the excess thionylchloride is distilled out in vacuo. The resulting material is used without further purification.

4790

Example 31B{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester

Using the procedure of Example 29B but replacing the resultant product from Example 29A with the resultant product from Example 31A affords the title compound.

4795

Example 31C{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester, alternate procedure

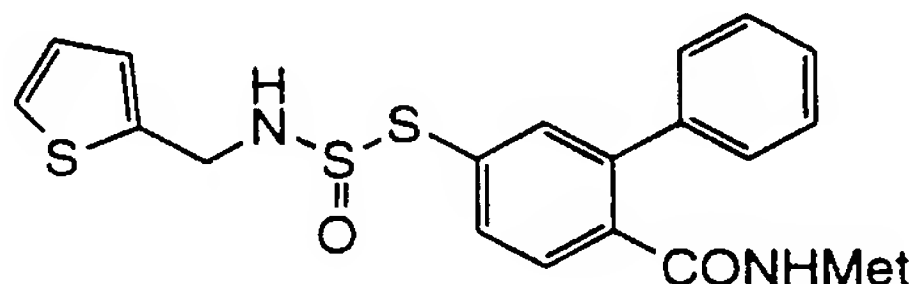
Using the procedure of Example 29C but replacing phosgene in toluene with thionyl chloride affords the title compound.

4800

Example 31D{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

The resultant compound from Example 31B is hydrolyzed according to the procedure of Example 1B to give the title product.

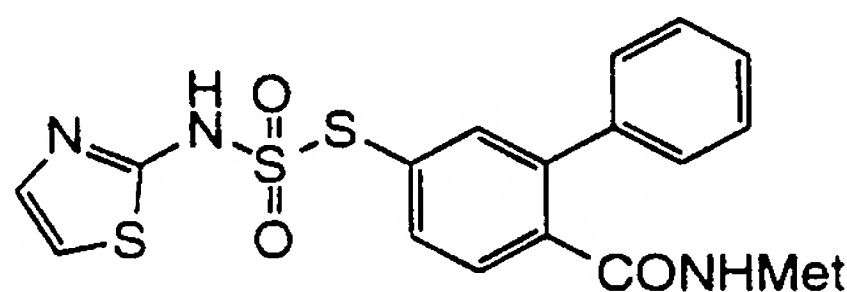
4805

Example 32

4810

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthio]benzoyl}-methionine

Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

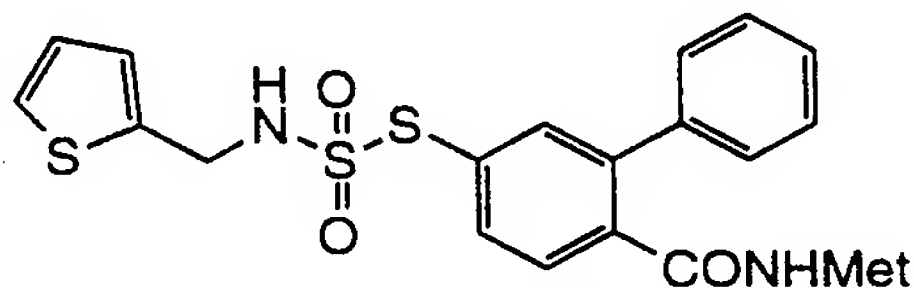


4815

Example 33{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthio]benzoyl}-methionine methyl ester

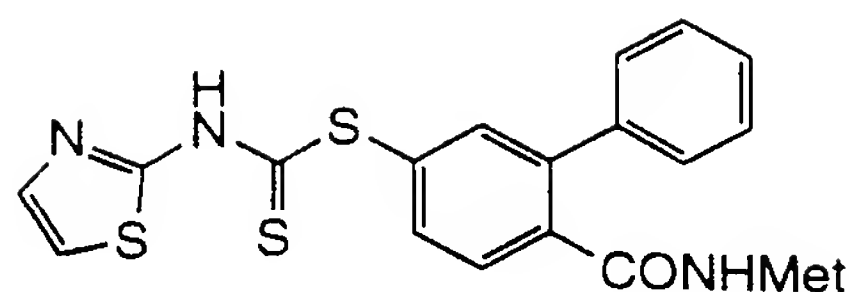
Using the procedure of Example 31 but replacing thionyl chloride with sulfonyl chloride affords the title product.

4820

Example 34{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthio]benzoyl}-methionine

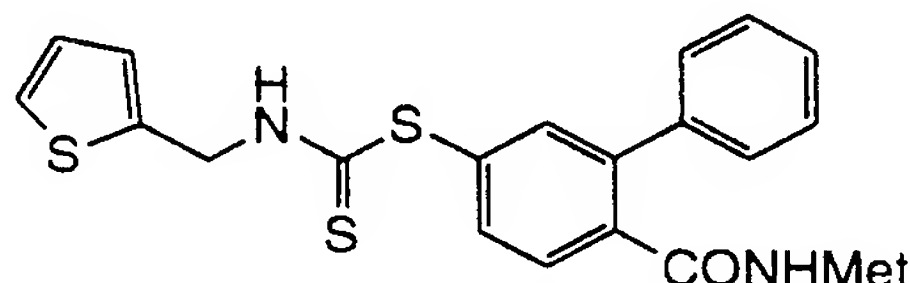
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine and replacing thionyl chloride with sulfonyl chloride affords the title product.

4825

Example 35

4830 {2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

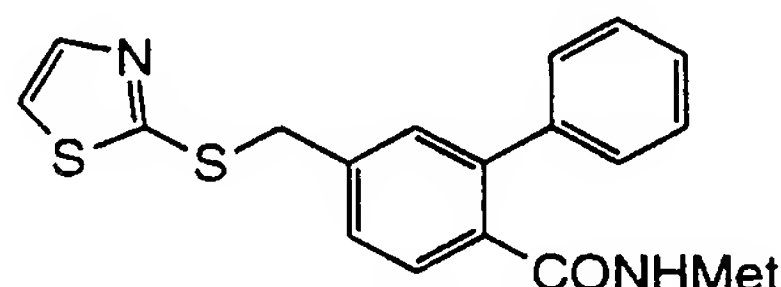
Example 36

4835

{2-Phenyl-4-[(thien-2-ylmethylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4840

Example 37

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

4845

Example 37A

{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester

The resultant product from Example 27A is dissolved DMF/water (2/1), and sodium hydrosulfide (5 equivalent) is added to the reaction mixture. The reaction is stirred until

4850 TLC analysis shows that the reaction is complete. Then, the reaction mixture is acidified with 3 N HCl to about pH 4, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified with column chromatography on silica gel to give the title compound.

4855

Example 37B

{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester, alternate procedure



To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16D (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K<sub>2</sub>CO<sub>3</sub> (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

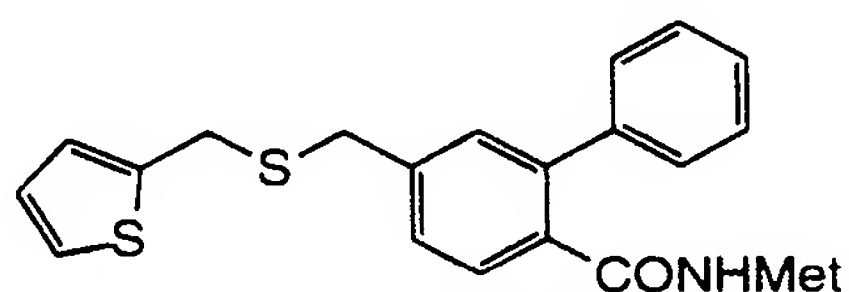
#### Example 37C

##### {2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine methyl ester

A mixture of the resultant thiol from Example 37A (1 mmol), 2-bromothiazole (1.5 mmol), and anhydrous potassium carbonate (5 mmol) in DMF is stirred at 100 °C until TLC analysis shows that the starting thiol disappeared. Then, the reaction mixture is diluted with water, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by column chromatography on silica gel to give the title compound.

##### {2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

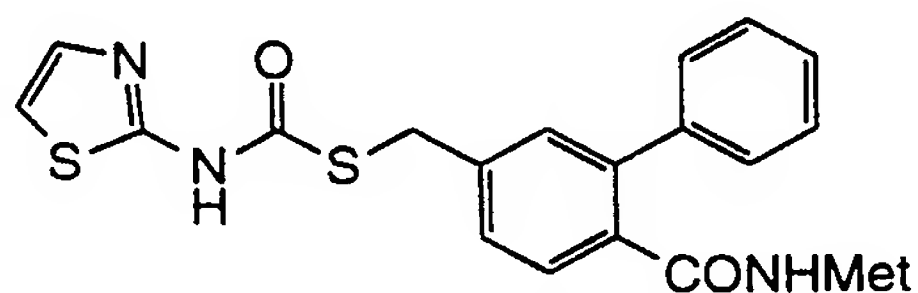
The resultant compound from Example 37C is hydrolyzed according to the procedure of Example 1B to give the title product.



#### Example 38

##### {2-Phenyl-4-[(thien-2-ylmethyl)thiomethyl]benzoyl}-methionine

Using the procedure of Example 37 and replacing 2-bromothiazole with 2-bromomethylthiophene affords the title product.

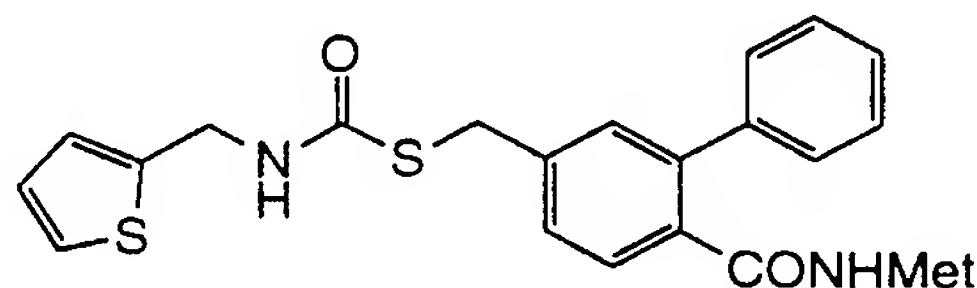


#### Example 39



{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

4890 Using the procedure of Example 29 with the resultant product from Example 37A affords the title product.

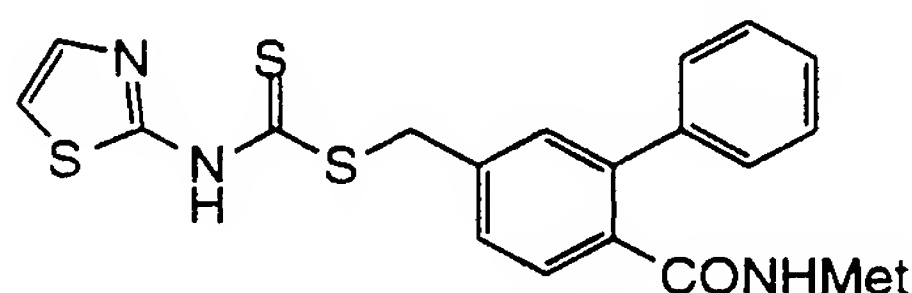


4895 Example 40

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylaniline affords the title product.

4900

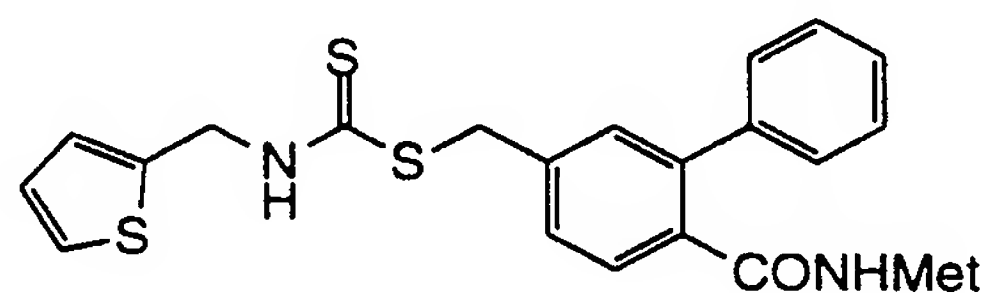


Example 41

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

4905

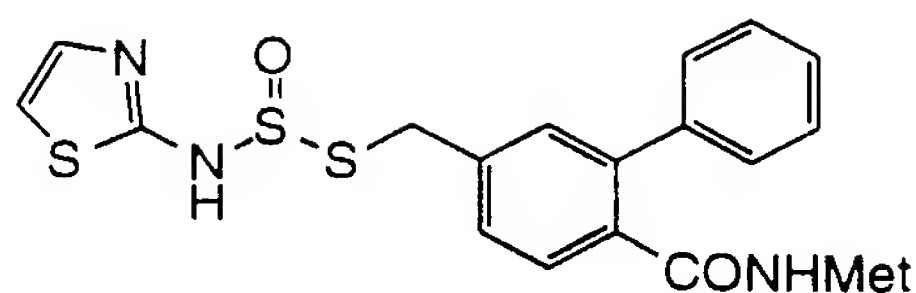


4910 Example 42

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

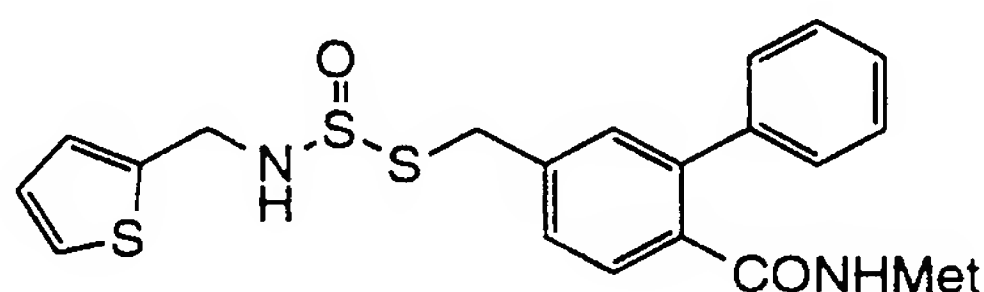
Using the procedure of Example 29 with the resultant product from Example 37A, replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol), and replacing 2-aminothiazol with thien-2-ylmethylaniline affords the title product.

4915

Example 43

4920 {2-Phenyl-4-[(thiazol-2-ylamino)thionylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A affords the title product.



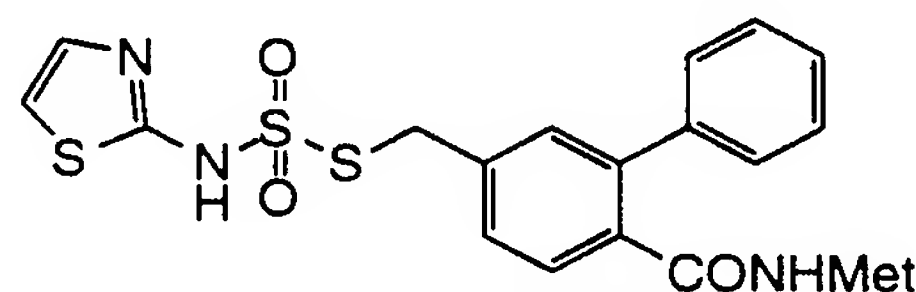
4925

Example 44

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthiomethyl]benzoyl}methionine

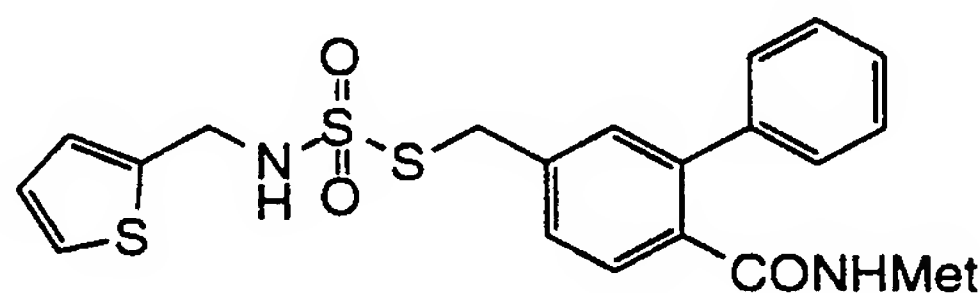
Using the procedure of Example 31 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4930

Example 45

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthiomethyl]benzoyl}-methionine

4935 Using the procedure of Example 31 with the resultant product from Example 37A and replacing thionyl chloride with sulfonyl chloride affords the title product. affords the title product.

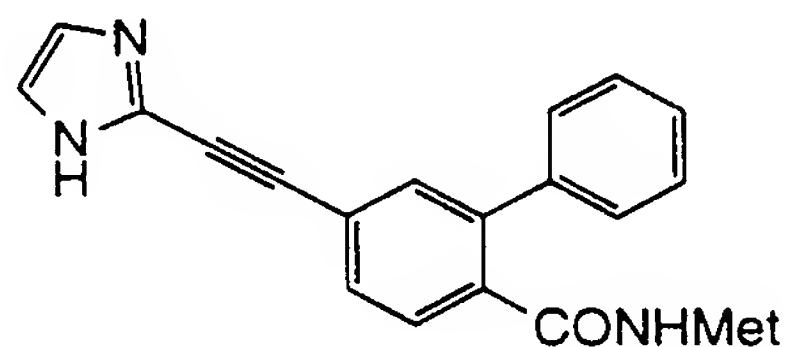


4940

Example 46

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A, replacing thionyl chloride with sulfuryl chloride, and replacing 2-aminothiazol with thien-2-ylmethylaniline affords the title product.



Example 47

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}methionine

Example 47A

(4-Ethynyl-2-phenylbenzoyl)methionine methyl ester

A mixture of (2-phenyl-4-bromobenzoyl)-methionine methyl ester (100 mmol), diethylamine (300 mmol), trimethylsilylacetylene (110 mmol), bis(triphenylphosphine) palladium diacetate (5 mmol) and copper(I) iodide (3 mmol) in toluene is heated at 60 °C until TLC analysis indicates the starting methyl ester has disappeared. The reaction mixture is concentrated in vacuo, redissolved in ether, filtered through silica gel, and concentrated. The residue is then dissolved in THF, and is treated with tetrabutylammonium fluoride (120 mmol). After TLC analysis indicates that no starting material is left, the reaction mixture is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified with column chromatography on silica gel to give the title product.

Example 47B

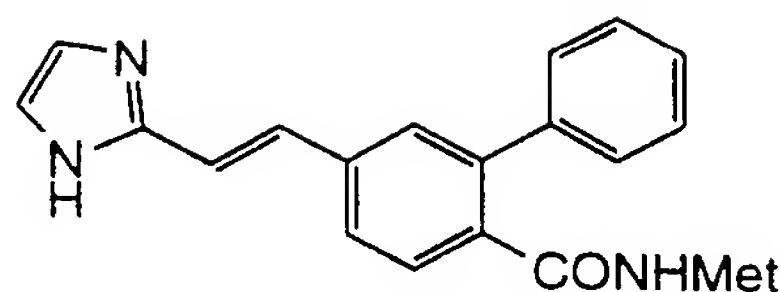
{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

The resultant product from Example 47A (5 mmol) is mixed with 4-bromoimidazole (5 mmol), diethylamine (1 mL), bis(triphenylphosphine) palladium diacetate (0.1 mmol) and copper(I) iodide (0.1 mmol) in toluene. The mixture is stirred at 25 °C until TLC analysis indicates the reaction is complete. The reaction mixture is concentrated in vacuo, and the residue is purified with column chromatography on silica gel to give the title product.

Example 47C

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine

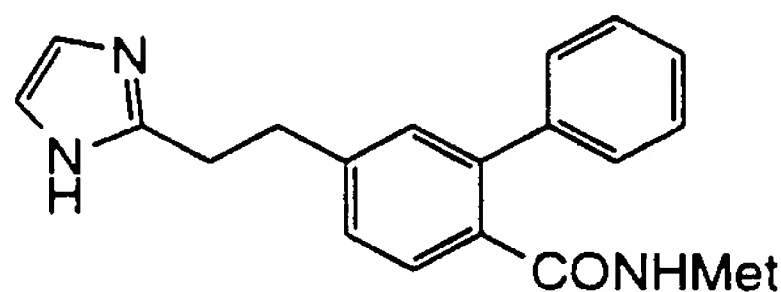
The resultant compound from Example 47B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 48

{4-[2-(Imidazol-4-yl)ethenyl]-2-phenylbenzoyl}-methionine

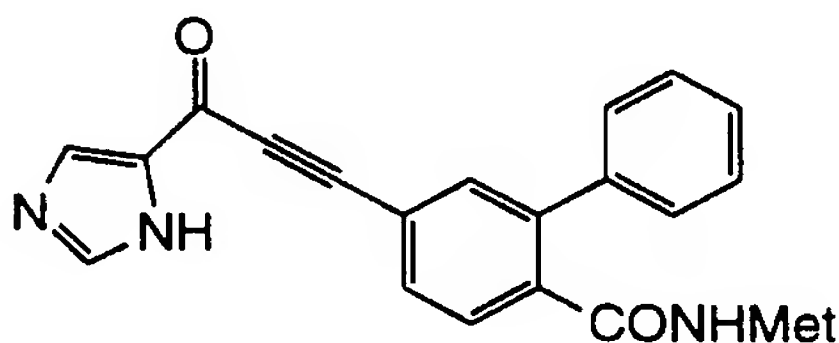
The resultant acetylene (3 mmol) from Example 47 is mixed with Lindlar catalyst (50 mg), 5 drops of quinoline in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 49

{4-[2-(Imidazol-4-yl)ethyl]-2-phenylbenzoyl}-methionine

The resultant olefin (1 mmol) from Example 48 is mixed with 5% palladium on carbon, (100 mg) in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 50

{4-[2-(Imidazol-4-yl)carbonyl]ethynyl]-2-phenylbenzoyl}-methionine

Example 50A

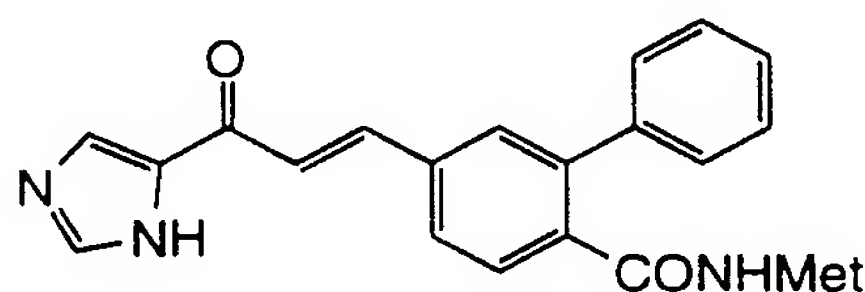
{4-[2-(Imidazol-4-yl)carbonyl]ethynyl]-2-phenylbenzoyl}-methionine methyl ester

5005 A stainless autoclave containing the resultant product from Example 47A (5 mmol), 4-bromoimidazole (5 mmol), 1,1'-bis(diphenylphosphine)-ferrocenepalladium dichloride (0.1 mmol), and triethylamine (10 mL) is flushed with nitrogen, and pressurized to 20 atm with carbon monoxide. The reaction mixture is stirred at 120 °C until judged complete by TLC analysis. After cooling, the triethylamine is evaporated in vacuo, and the residue is purified  
5010 by column chromatography on silica gel to give the title compound.

#### Example 50B

##### {4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

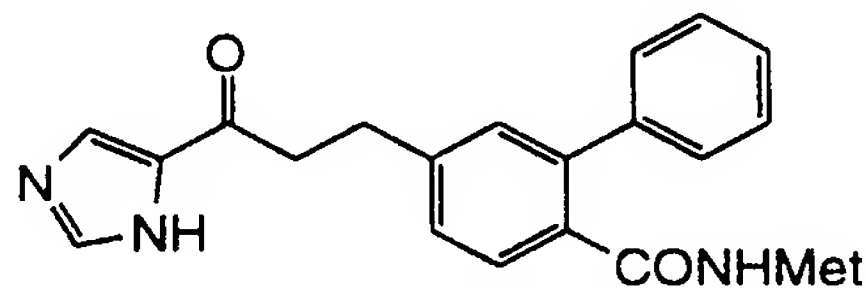
5015 The resultant compound from Example 50A is hydrolyzed according to the procedure of Example 1B to give the title product.



#### Example 51

##### {4-[2-(Imidazol-4-ylcarbonyl)ethenyl]-2-phenylbenzoyl}-methionine

5020 Using the procedure of Example 48 with the resultant compound from Example 50 affords the title product.



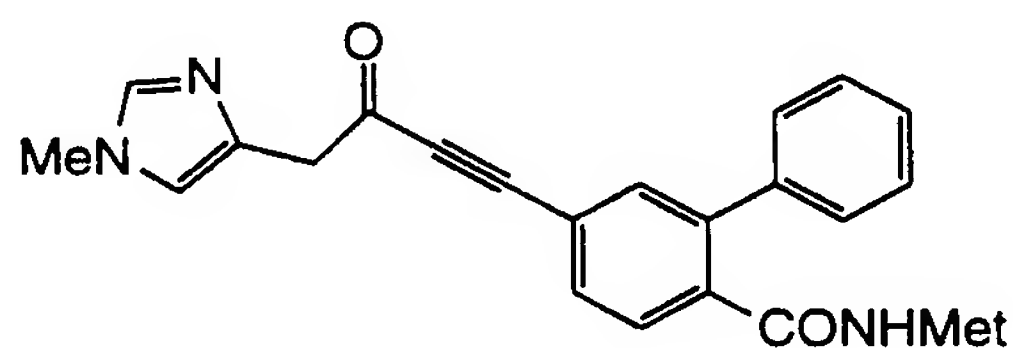
5025

#### Example 52

##### {4-[2-(Imidazol-4-ylcarbonyl)ethyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 51 affords the title product.

5030



#### Example 53

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}methionine

5035

### Example 53A

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine methyl ester

5040

To a solution of 1-methyl-4-imidazoleacetic acid (5 mmol) in methylene chloride at 0 °C is added oxalyl chloride (6 mmol) and DMF (0.05 mmol). After 30 minute, the solvent is evaporated in vacuo. The residue is redissolved in dichloromethane, followed by the addition of the resultant acetylene from Example 47A (5 mmol), triethylamine (10 mmol), and copper(I) iodide (1 mmol). The reaction is stirred at 25 °C until TLC analysis indicates no starting material is left in the reaction mixture. The reaction is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to give the title compound.

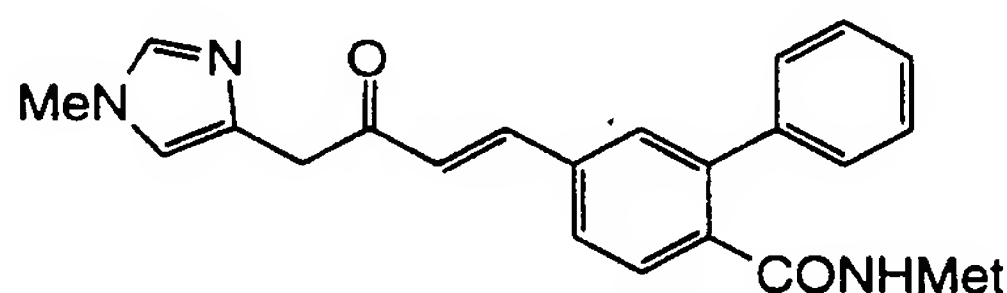
5045

### Example 53B

5050

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

The resultant compound from Example 53A is hydrolyzed according to the procedure of Example 1B to give the title product.



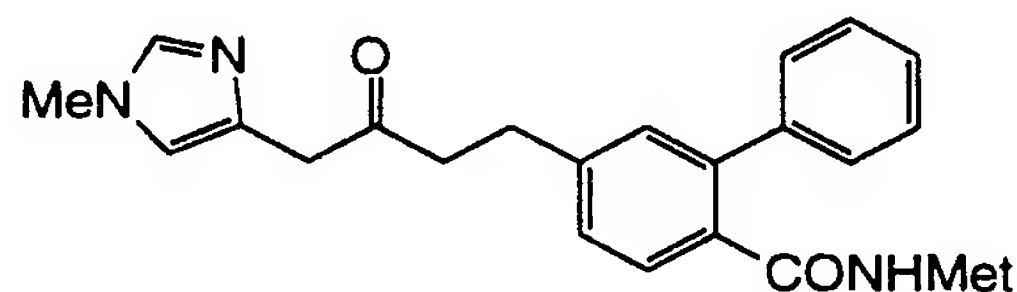
5055

### Example 54

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butenyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 53 affords the title product.

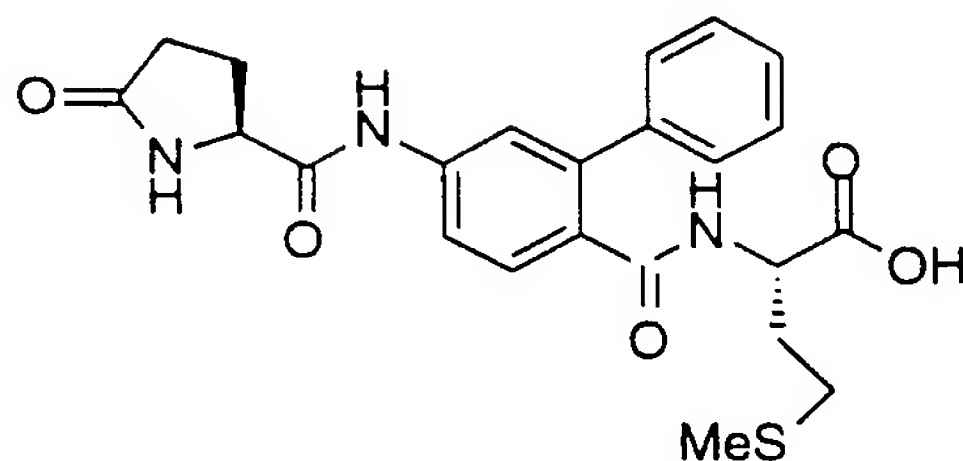
5060



### Example 55

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyl]-2-phenylbenzoyl}-methionine

5065 Using the procedure of Example 49 with the resultant compound from Example 53 affords the title product.



5070

Example 56

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Example 56A

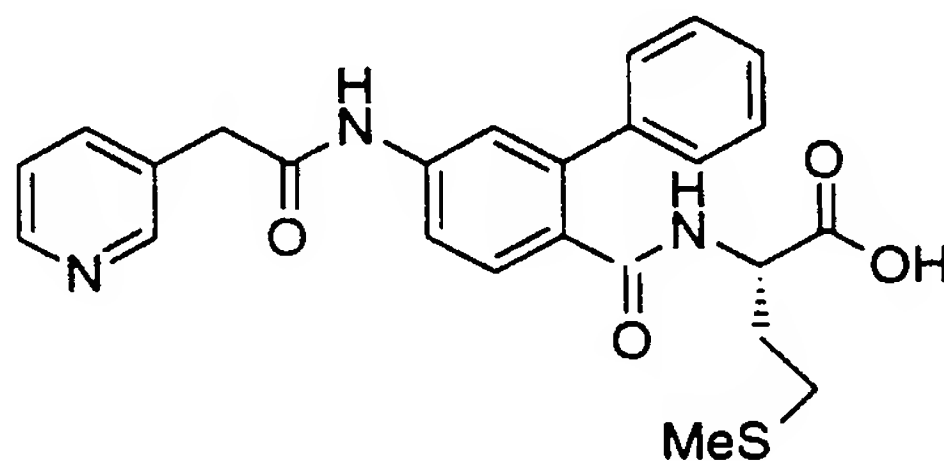
(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine methyl ester

5075 To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N  
5080 HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 56B

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

5085 The resultant compound from Example 56A is hydrolyzed according to the procedure of Example 1B to give the title product.



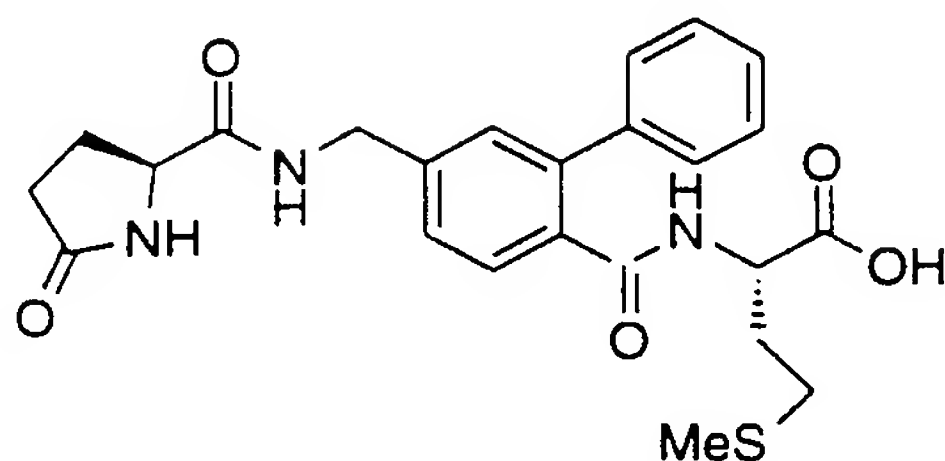
5090

Example 57

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Using the procedure of Example 56 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.

5095

Example 58

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

5100

Example 58A

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine methyl ester

To a solution of the resultant amine from Example 18B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

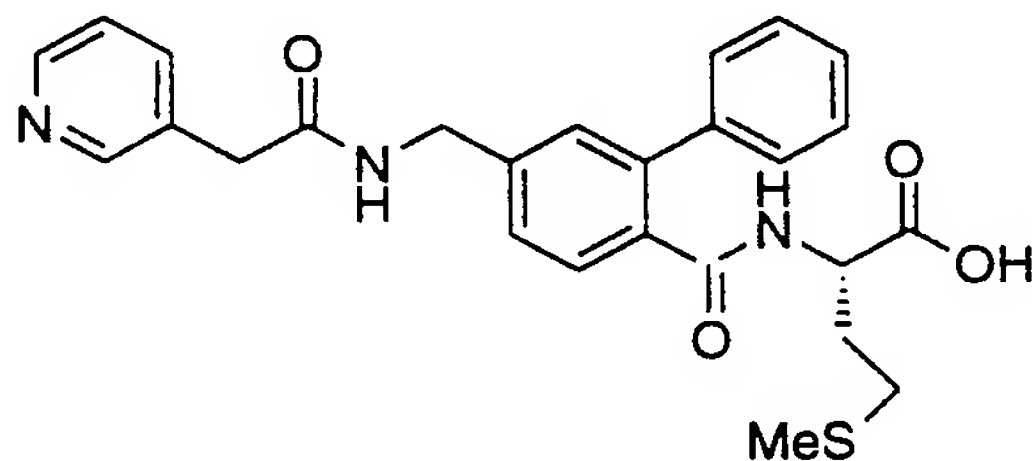
5110

Example 58B

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

The resultant compound from Example 58A is hydrolyzed according to the procedure of Example 1B to give the title product.

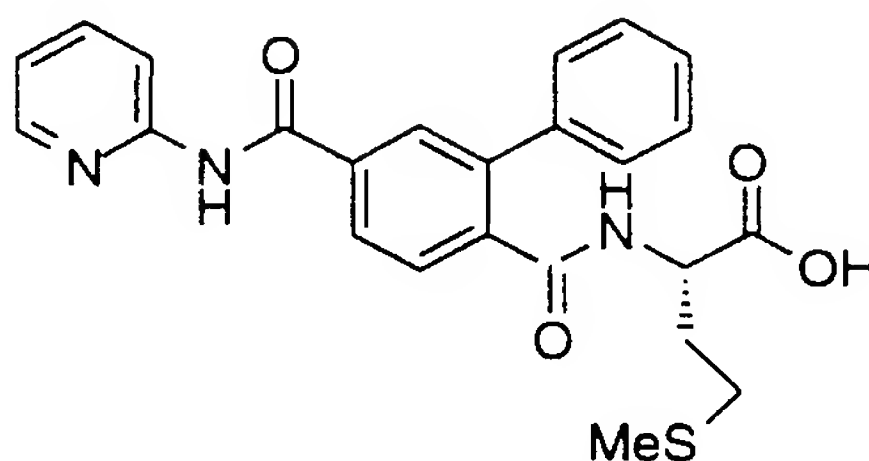
5115

Example 59

naming error(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine



5120 Using the procedure of Example 58 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



Example 60

5125 4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

Example 60A

4-Carboxy-2-phenylbenzoyl methionine methyl ester

5130 A solution of 4-bromo-2-phenylbenzoyl methionine methyl ester (1.0 equivalent), Pd(OAc)<sub>2</sub> (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

5135 Example 60B

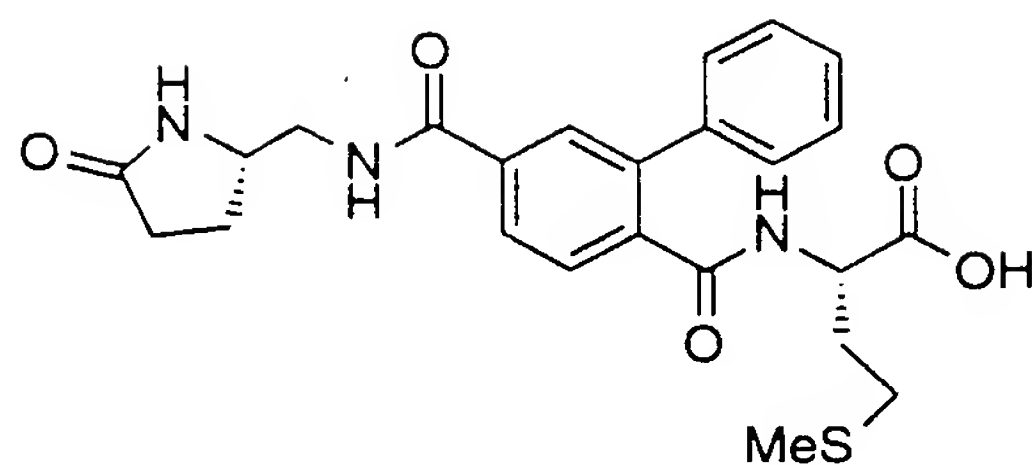
4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine methyl ester

5140 To a solution of the resultant acid from Example 60A (1.0 equivalent) in DMF is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 60C

5145 4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

The resultant compound from Example 60B is hydrolyzed according to the procedure of Example 1B to give the title product.

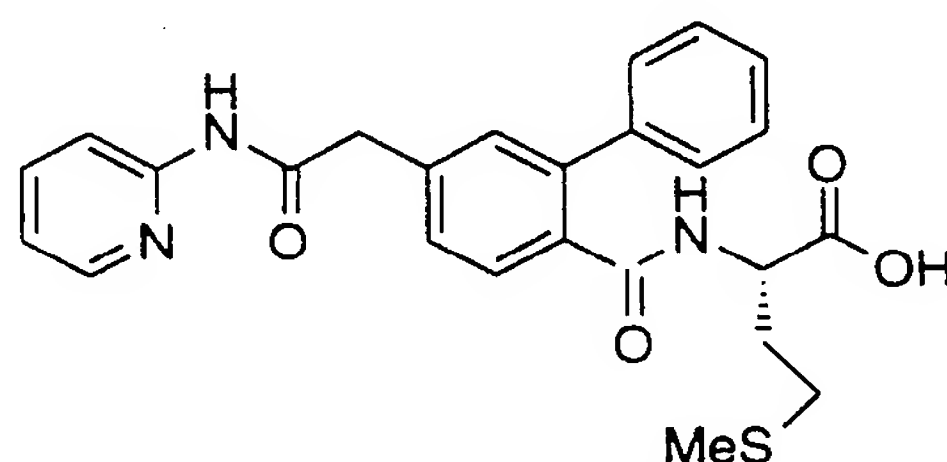


5150

Example 614-((S)-2-Pyrrolidone-5-aminomethyl)carbonyl-2-phenylbenzoyl methionine

Using the procedure of Example 60 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

5155

Example 624-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

5160

Example 62A4-Diazocarbonyl-2-phenylbenzoyl methionine methyl ester

The resultant acid from Example 60A (1 equivalent) in dichloromethane is treated with oxalyl chloride (1 equivalent) and DMF (0.05 equivalent). When gas evolution has ceased, the acid chloride solution is added to an ether solution of diazomethane. The reaction is stirred until judged complete by TLC analysis, and then is concentrated to give the crude title compound which is purified by chromatography on silica gel.

5165

Example 62B4-carboxymethyl-2-phenylbenzoyl methionine methyl ester

5170

The resultant compound from Example 62A (1 equivalent) in dioxane is added to a slurry of sodium thiosulfate (1.1 equivalents) and silver (I) oxide (0.5 equivalent) in water. The reaction is stirred until judged complete by TLC analysis, filtered, acidified, and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title product.

5175

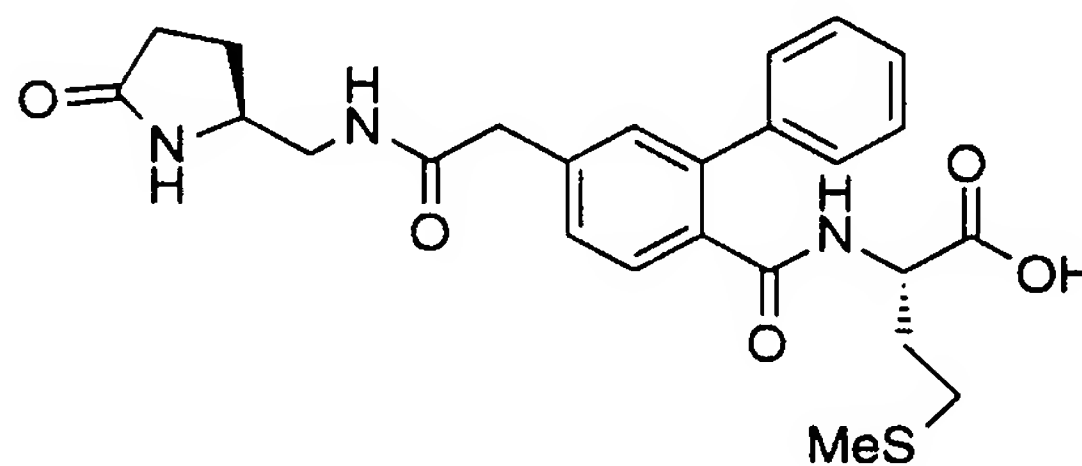
Example 62C

4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine methyl ester

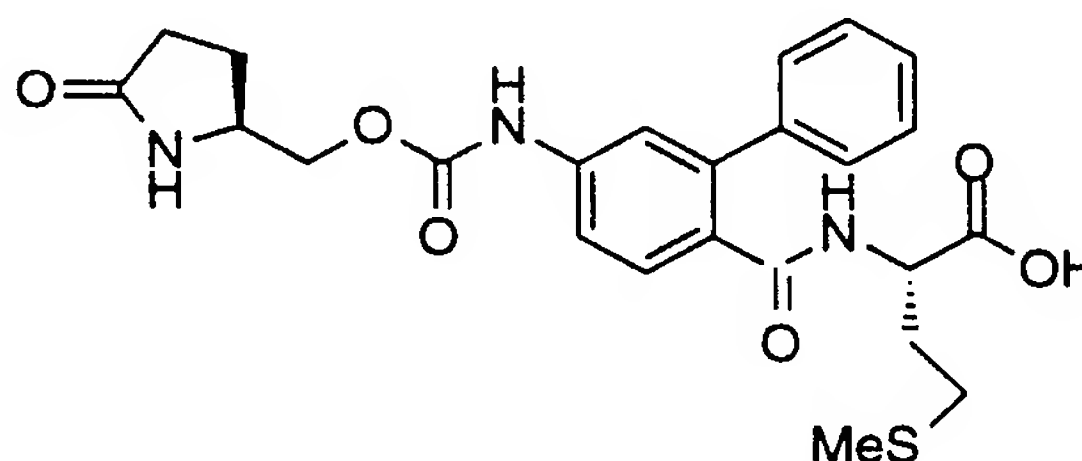
To a solution of the resultant acid from Example 62B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 62D4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

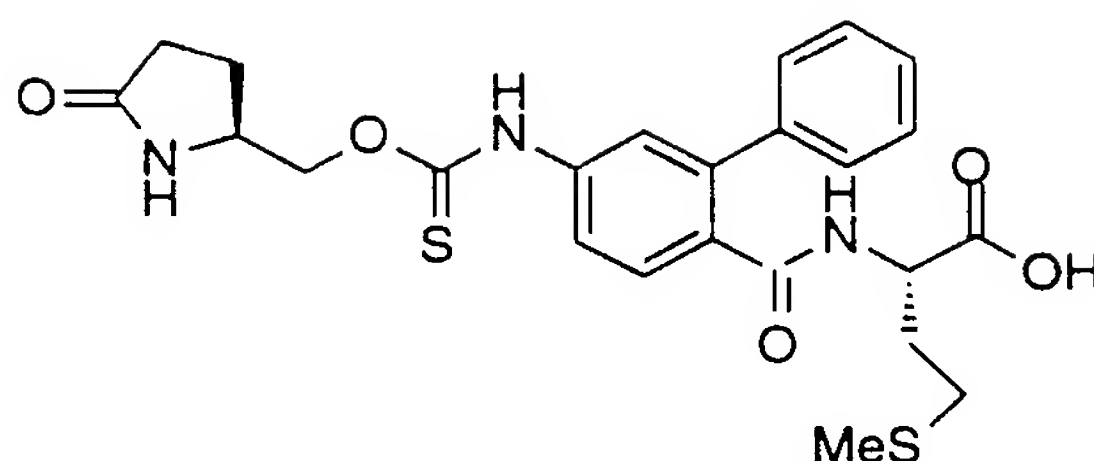
The resultant compound from Example 62C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 634-((S)-2-Pyrrolidone-5-aminomethyl)carbonylmethyl)-2-phenylbenzoyl methionine

Using the procedure of Example 62 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

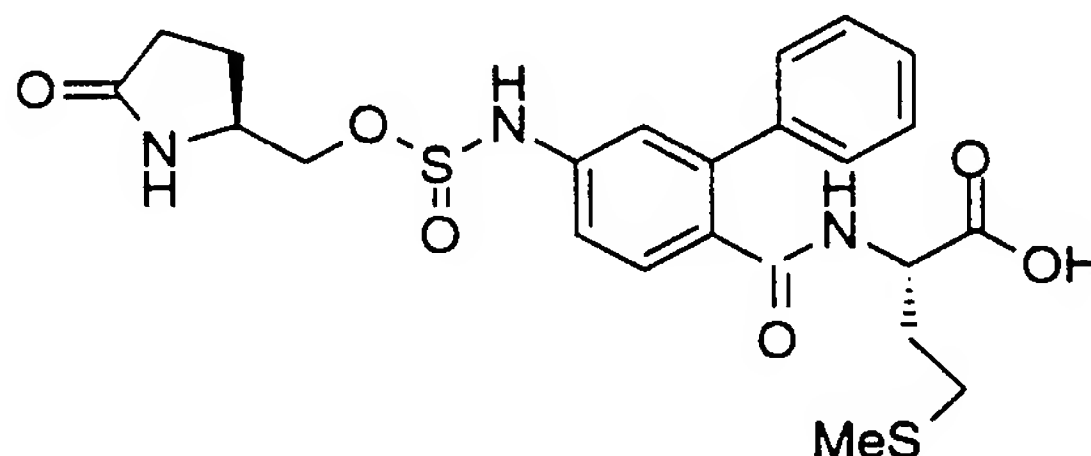
Example 644-((S)-2-Pyrrolidone-5-methoxycarbonylamino)-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 655210 4-((S)-2-Pyrrolidone-5-methoxythiocarbonyl)amino-2-phenylbenzoyl methionine

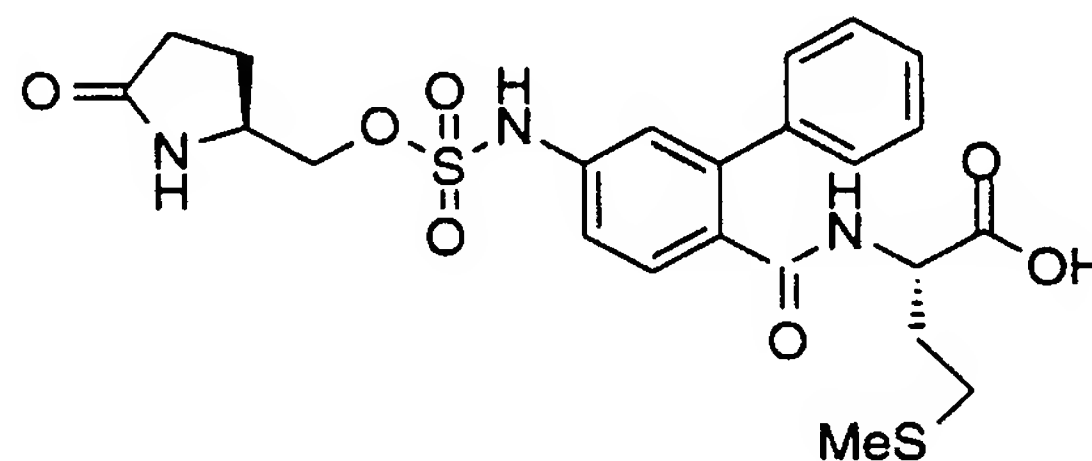
The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

5215

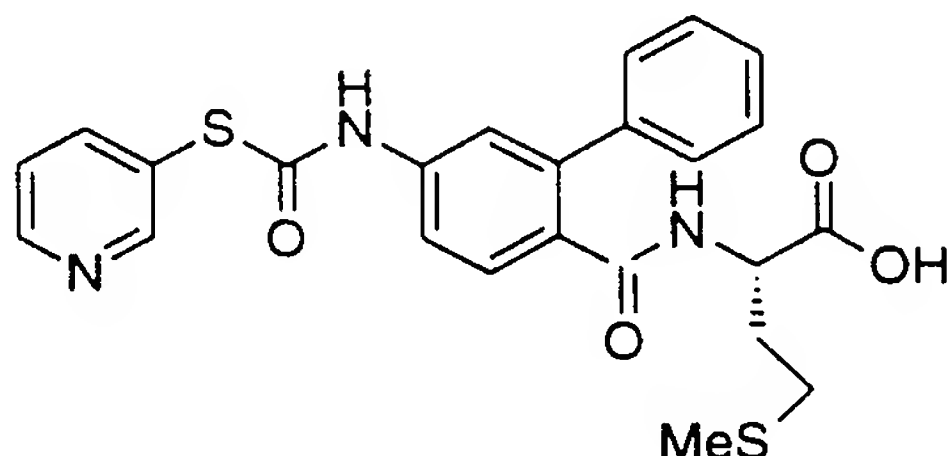
Example 664-((S)-2-Pyrrolidone-5-methoxysulfinyl)amino-2-phenylbenzoyl methionine

5220 The title compound is prepared as described in Example 3 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

5225

Example 674-((S)-2-Pyrrolidone-5-methoxysulfonyl)amino-2-phenylbenzoyl methionine

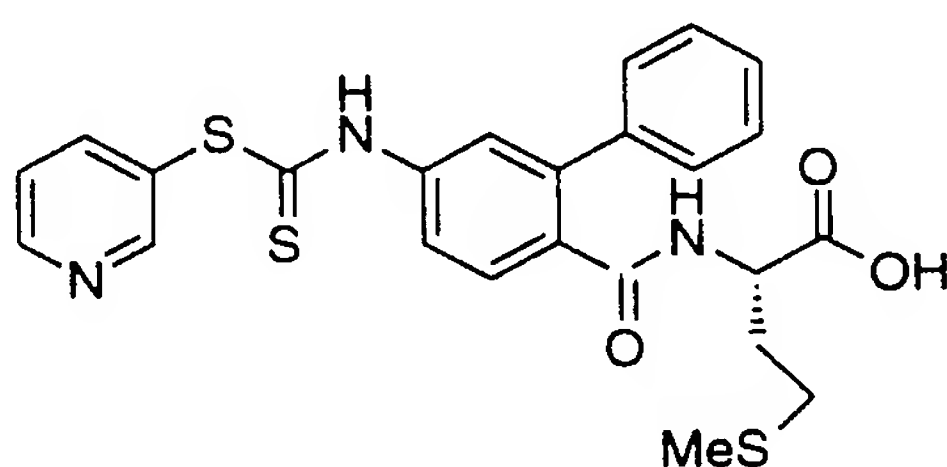
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 68

4-(Pyridin-3-ylmercaptocarbonyl)amino-2-phenylbenzoyl methionine

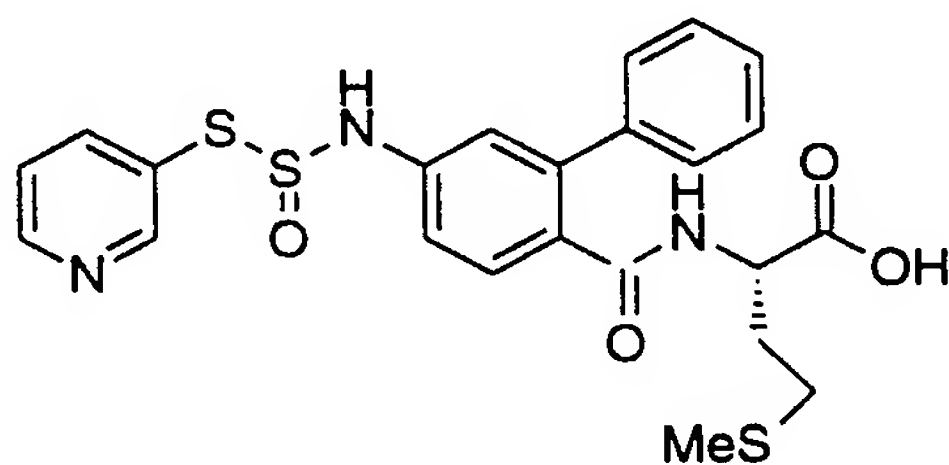
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 69

4-(Pyridin-3-ylmercaptothiocabonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

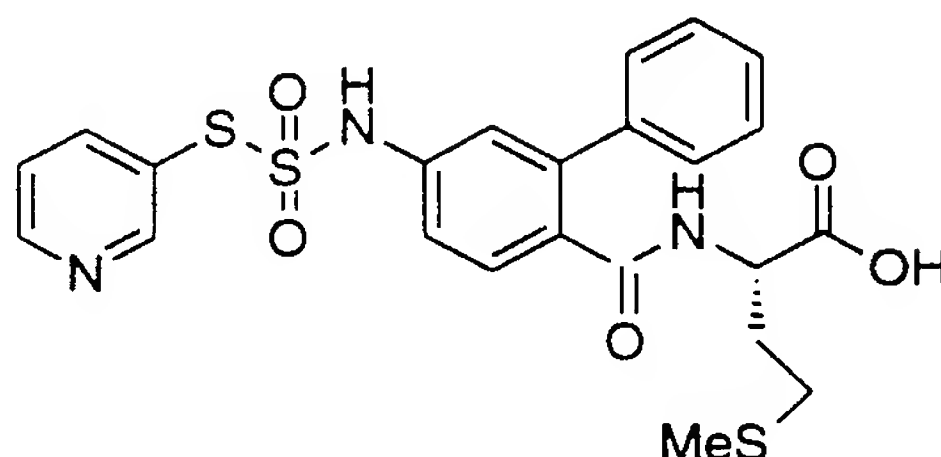


Example 70

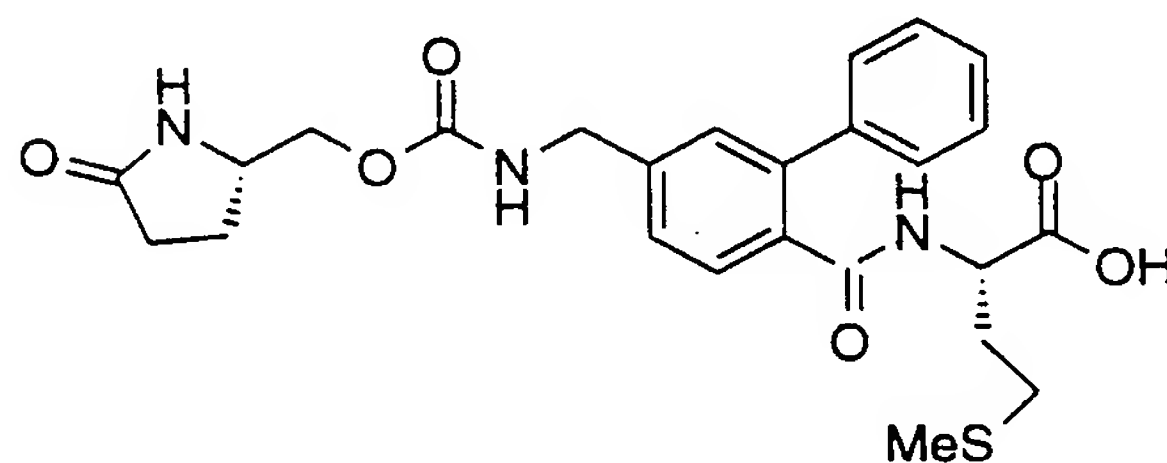
4-(Pyridin-3-ylmercaptosulfinyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5255

Example 714-(Pyridin-3-ylmercaptosulfonyl)amino-2-phenylbenzoyl methionine

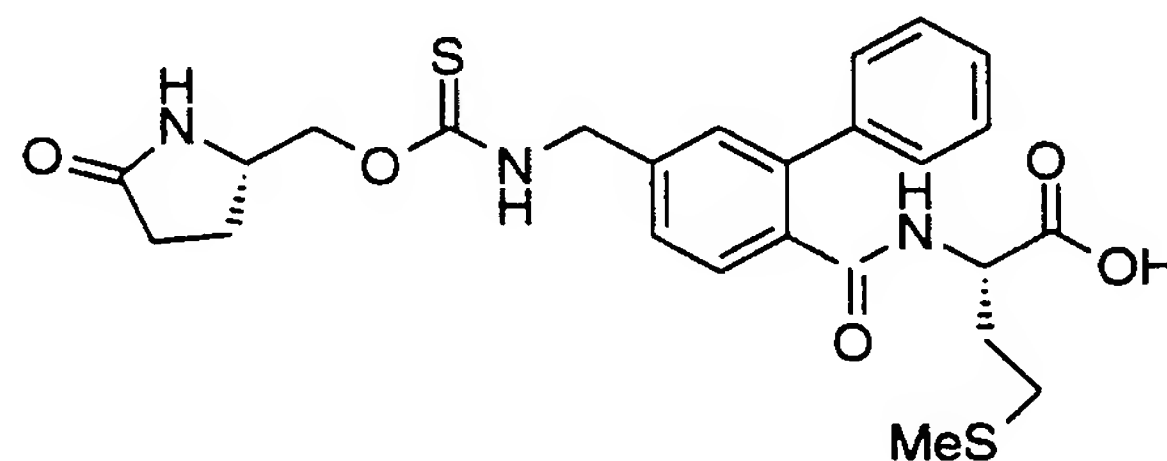
5260 The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



5265

Example 724-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)aminomethyl-2-phenylbenzoyl methionine

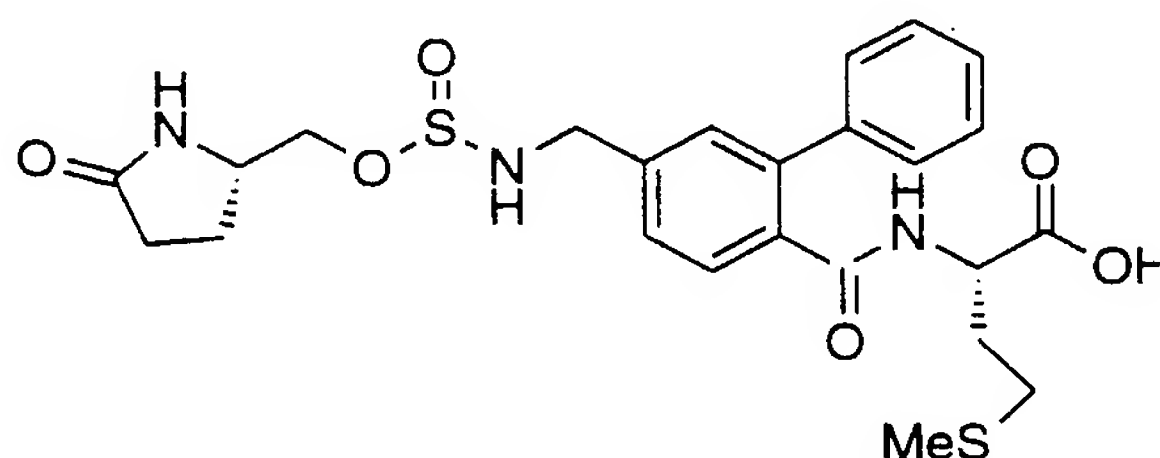
5270 The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 73

5275 4-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

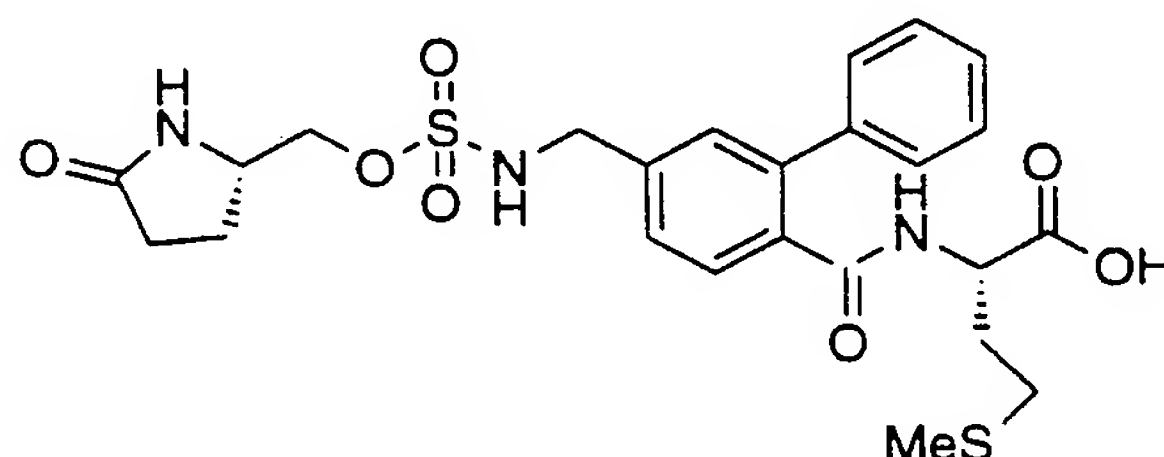
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

5280

Example 744-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)aminomethyl-2-phenylbenzoyl methionine

5285

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



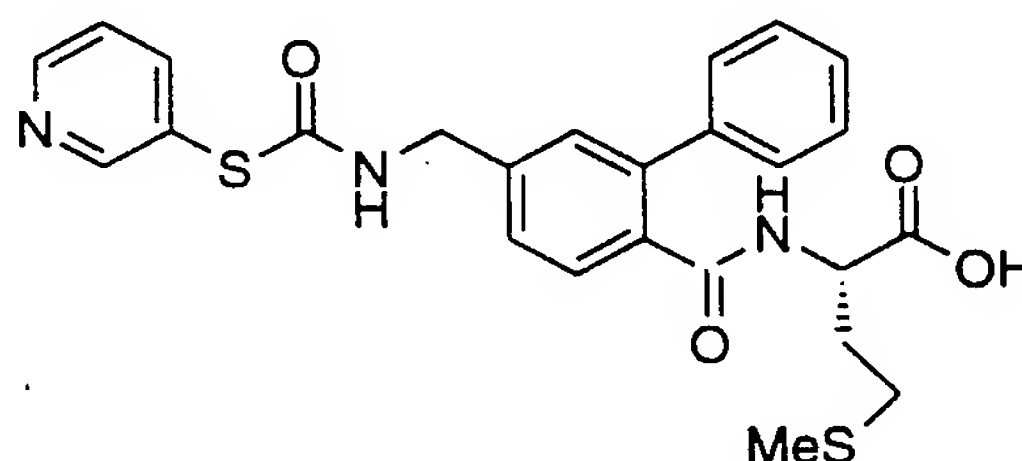
5290

Example 754-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is

5295

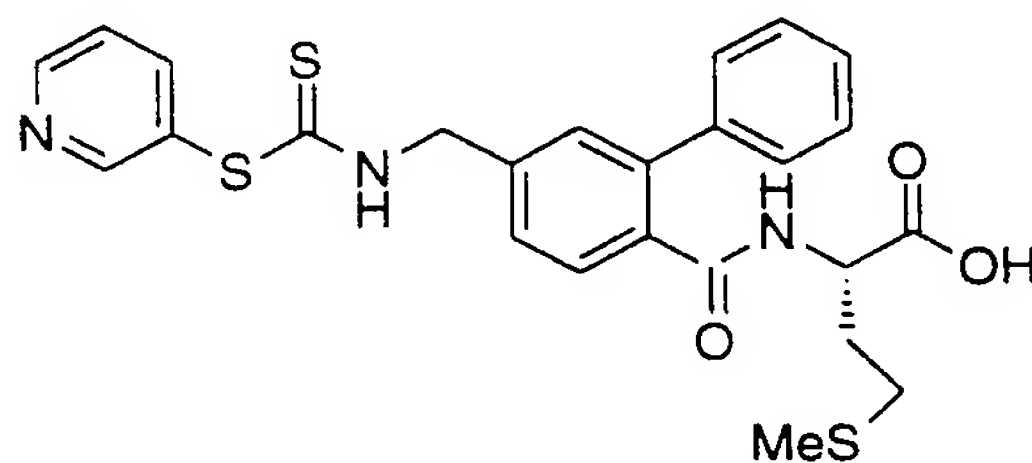
replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 76

5300 4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

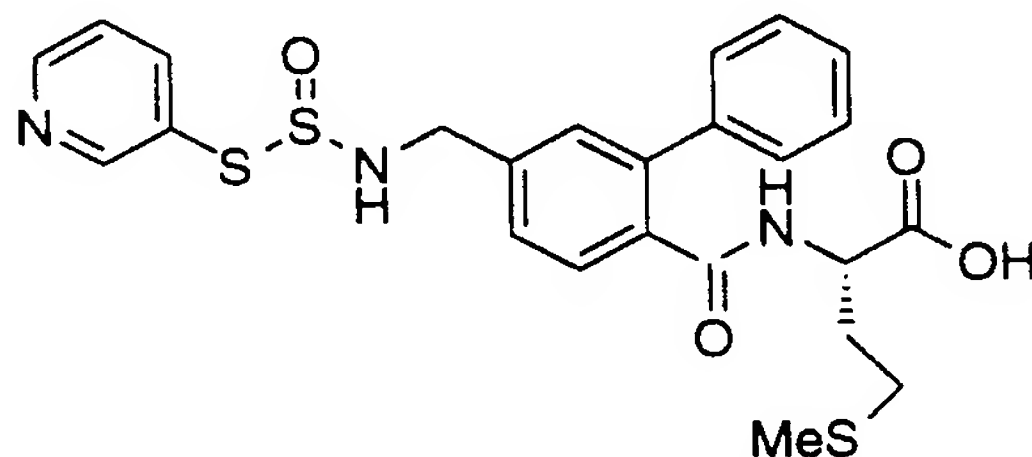
5305



Example 77

4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

5310 The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



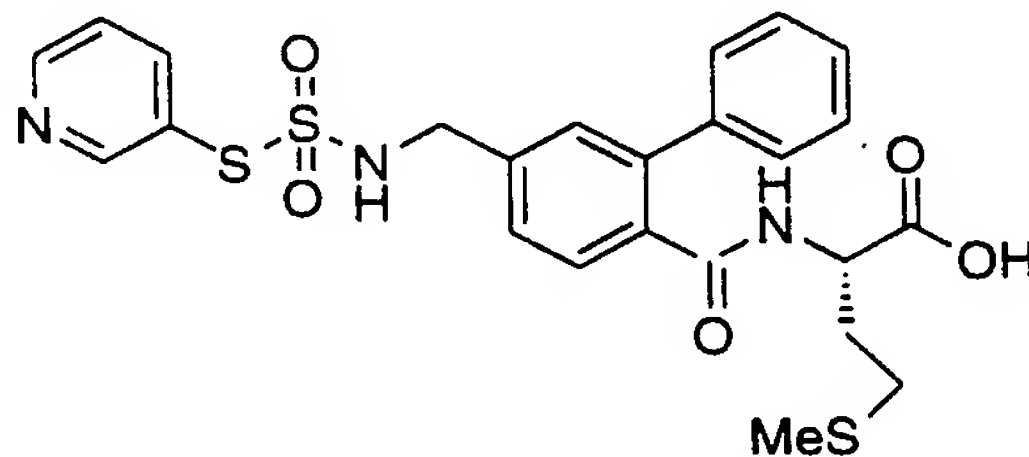
Example 78

5315

4-(Pyridin-3-ylmercaptosulfinyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5320



Example 79



4-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

5325 The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5330

Example 80A-NH-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products  
5335 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.  
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-  
5340 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 81A-NH-CS-NH-B

5345 The procedure of Example 1 is used with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206  
5350 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.  
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-  
5355 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 82A-NH-SO-NH-B

5360 The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (*S*)-5-

aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5365 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5370

Example 83A-NH-SO<sub>2</sub>-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For 5375 products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the 5380 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5385

Example 84A-NH-SO<sub>2</sub>-B

The procedure of Example 5 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products 5390 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5395

Example 85A-NH-CO-O-B

The anilines from Table 1 (B-NH<sub>2</sub>) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 86

##### A-NH-CS-O-B

The anilines from Table 1 (B-NH<sub>2</sub>) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 87

##### A-NH-SO-O-B

The anilines from Table 1 (B-NH<sub>2</sub>) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5435

Example 88A-NH-SO<sub>2</sub>-O-B

The anilines from Table 1 (B-NH<sub>2</sub>) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5450

Example 89A-NH-CH<sub>2</sub>-B

The procedure of Example 16 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5460

Example 90A-NH-CO-NH-CH<sub>2</sub>-B

5465

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5470

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 91

##### A-NH-CS-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 92

##### A-NH-SO-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 93

##### A-NH-SO<sub>2</sub>-NH-CH<sub>2</sub>-B



5510 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by sulfuryl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5520 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 94

##### A-NH-CO-O-CH<sub>2</sub>-B

5525 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5530 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 95

##### A-NH-CS-O-CH<sub>2</sub>-B

5540 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5545 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 96

A-NH-CO-S-B

5550 The anilines Table 1 (B-NH<sub>2</sub>) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from  
5555 amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5560

Example 97

A-NH-CS-S-B

The anilines Table 1 (B-NH<sub>2</sub>) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of  
5565 Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5570 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5575

Example 98

A-NH-SO-S-B

The anilines Table 1 (B-NH<sub>2</sub>) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of  
5580 Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from

amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5585 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5590 Example 99

A-NH-SO<sub>2</sub>-S-B

The anilines Table 1 (B-NH<sub>2</sub>) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfur chloride and 5595 2-aminothiazol is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the 5600 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 100

5605 A-NH-CO-S-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine 5610 from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the 5615 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 101

5620

A-NH-CS-S-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

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This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 102

5635

A-NH-SO-S-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5640

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This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 103

5650

A-NH-SO<sub>2</sub>-S-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products

5655

derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 104

##### A-CO-NH-B

The procedure of Example 56 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and pyroglutamic acid is replaced by an acid from Table 4 (A-CO<sub>2</sub>H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 105

##### A-CO-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 58 with the exception that pyroglutamic acid is replaced by an acid from Table 4 (A-CO<sub>2</sub>H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 106

##### A-CO-C $\equiv$ C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 53 with the exception that 1-methyl-4-imidazoleacetic acid is replaced by an acid from Table 4 (A-CO<sub>2</sub>H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 107

##### A-CO-CH=CH-B

The products from Example 106 are reacted according to the procedure of Example 54. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 108

##### A-CO-CH<sub>2</sub>-CH<sub>2</sub>-B

The products from Example 107 are reacted according to the procedure of Example 55. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5730 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 109

A-NH-CO-B

5735 The procedure of Example 60 is used with the exception that 4-bromo-2-phenylbenzoyl methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5740 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5745

Example 110

A-NH-CO-CH<sub>2</sub>-B

5750 The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 60A. The resultant carbocyclic acids are reacted according to the procedure of Example 62 with the exception that 2-aminopyridine is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5755 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5760

Example 111

A-CH<sub>2</sub>-NH-B

5765 The procedure of Example 25 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an amine from Table 1 (B-NH<sub>2</sub>) and 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is

followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

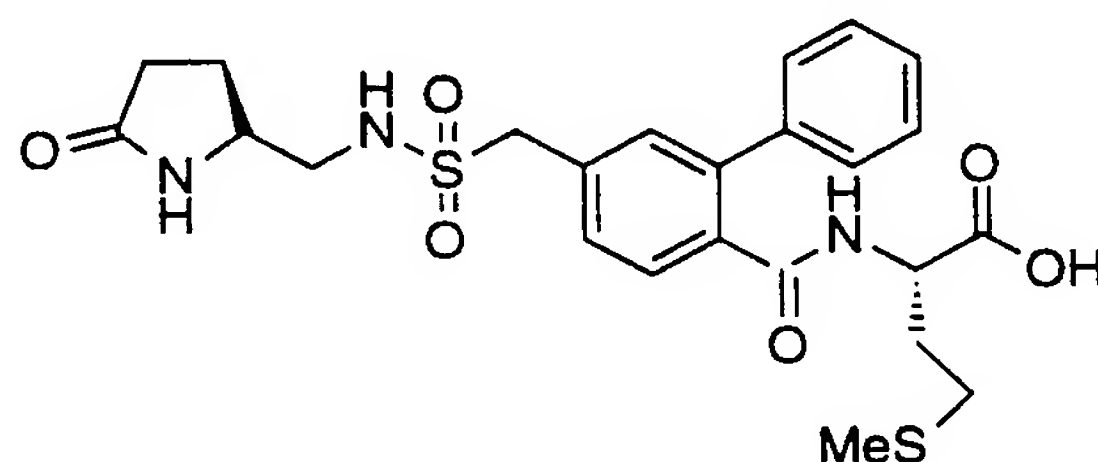
5770 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5775

Example 112  
A-CH<sub>2</sub>-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 25 with the exception that 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

5785 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



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Example 113  
4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl methionine



Example 113A4-Thioacetoxymethyl-2-phenylbenzoic acid methyl ester

5800 To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16B (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in  
5805 methanol and is treated with K<sub>2</sub>CO<sub>3</sub> (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 113B4-Chlorosulfonylmethylene-2-phenylbenzoic acid methyl ester

5810 The resultant compound from Example 113A in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

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Example 113C4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 113B (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0  
5820 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 113D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid

5825 The resultant compound from Example 113C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 113E4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine methyl ester

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To a solution of the resultant compound from Example 113D (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged

5835 complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

#### Example 113F

5840 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine

The resultant compound from Example 113E is hydrolyzed according to the procedure of Example 1B to give the title product.

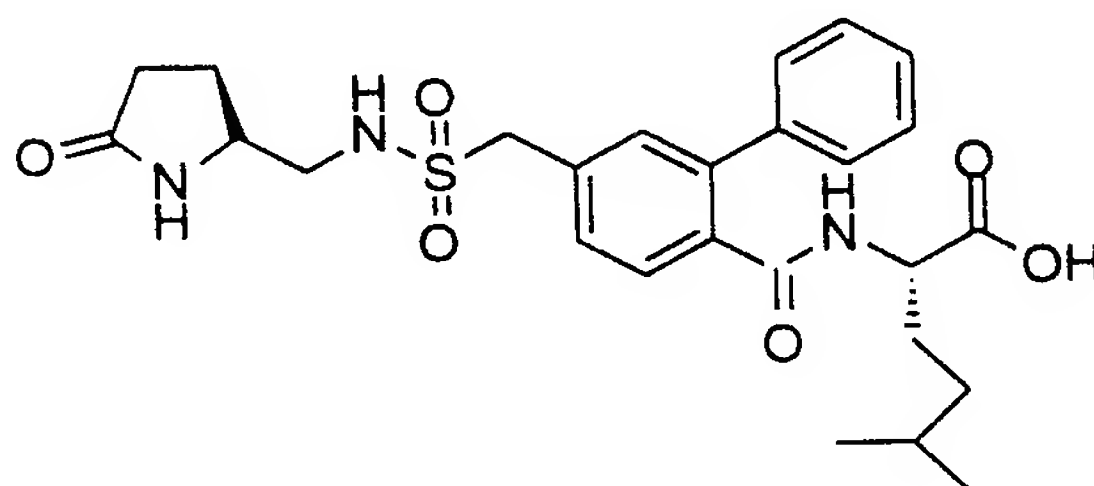
#### Example 114

5845

#### A-NH-SO<sub>2</sub>-CH<sub>2</sub>-B

The procedure of Example 113 is used with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on

5850 the fragment of the final compound that is derived from amines 146-206.



#### Example 115

5855 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl leucine

#### Example 115A

#### 4-(Hydroxymethyl)-2-phenylbenzoyl leucine methyl ester

(2-phenyl-4-bromobenzoyl)-leucine methyl ester is reacted according to the procedures of

5860 Example 16F-G.

#### Example 115B

#### 4-Thioacetoxymethyl-2-phenylbenzoyl leucine methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 115A (1. equivalent) in THF. The

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reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K<sub>2</sub>CO<sub>3</sub> (2 equivalents). When the reaction is judged to be  
5870 complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

#### Example 115C

##### 4-Chlorosulfonylmethylene-2-phenylbenzoyl leucine methyl ester

5875 The resultant compound from Example 115B in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

#### Example 115D

##### 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine methyl ester

To a solution of the resultant compound from Example 115C (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0  
5885 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

#### Example 115E

##### 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine

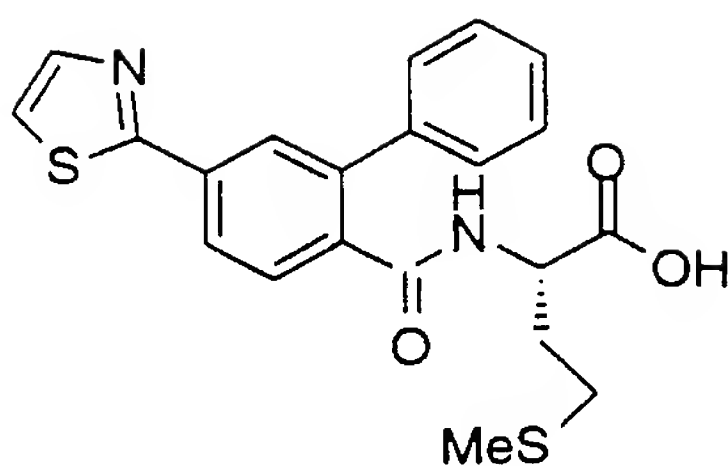
5890 The resultant compound from Example 115D is hydrolyzed according to the procedure of Example 1B to give the title product.

#### Example 116

##### A-NH-SO<sub>2</sub>-CH<sub>2</sub>-B

5895 The procedure of Example 115 is used with the exception that (2-phenyl-4-bromobenzoyl)-leucine methyl ester is replaced by a bromide from Table 2, entries 28-132 (B-Br) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes  
5900 the ester on the fragment of the final compound that is derived from amines 146-206.



Example 117

5905

4-(2-Thiazolyl)-2-phenylbenzoyl methionineExample 117A2-Thiazole boronic acid

5910

A solution of thiazole (1.0 equivalent) is lithiated with a slight excess of n-butyl lithium in THF (1.05 equivalents) and then treated with trimethyl borate (1.05 equivalents). The reaction mixture is quenched by the addition of aqueous HCl and the resulting boronate ester is cleaved by the addition of excess aqueous NaOH. After acidification and extraction into ethyl acetate the crude boronic acid is used without further purification.

5915

Example 117B4-(2-Thiazolyl)-2-phenylbenzoyl methionine methyl ester

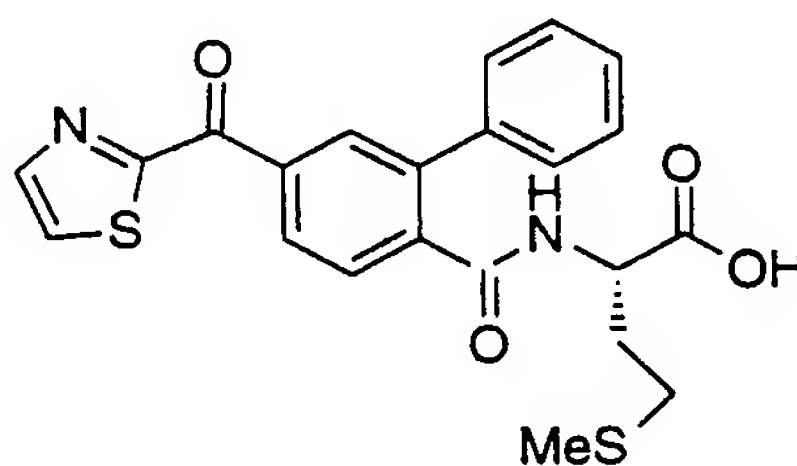
5920

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid (1.0 equivalent) and catalytic  $\text{Pd}(\text{PPh}_3)_4$  is heated in a two phase system of toluene and aqueous  $\text{Na}_2\text{CO}_3$ . After cooling, the resulting biaryl compound is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

Example 117C4-(2-Thiazolyl)-2-phenylbenzoyl methionine

5925

The resultant compound from Example 117C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 118

5930

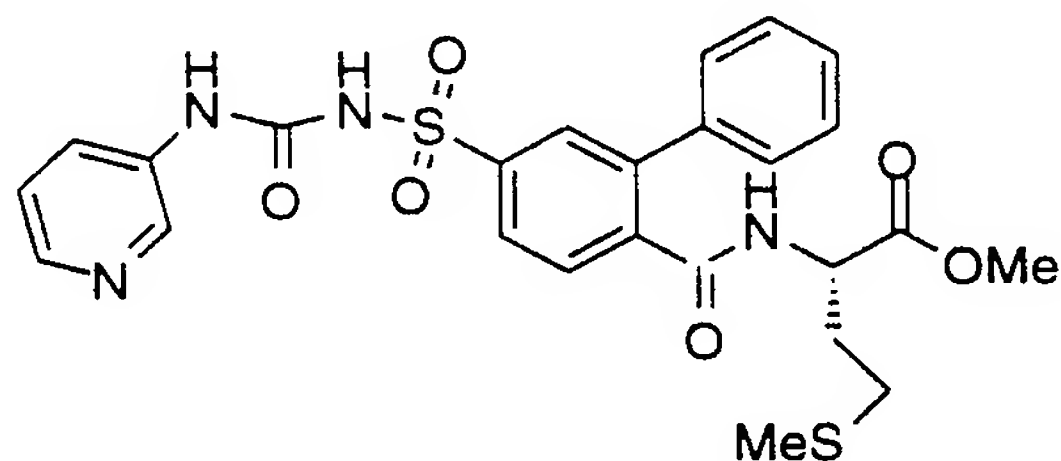
4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

Example 118A4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine methyl ester

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole  
 5935 boronic acid from Example 117A (1.0 equivalent) and catalytic  $\text{Pd}(\text{PPh}_3)_4$  is heated in a two  
 phase system of toluene and aqueous  $\text{Na}_2\text{CO}_3$  previously purged with a large excess of  
 carbon monoxide. The resulting diaryl ketone is isolated by evaporation of the organic  
 phase and is purified by chromatography on silica gel.

Example 118B4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

The resultant compound from Example 118A is hydrolyzed according to the procedure of  
 Example 1B to give the title product.

Example 1194-[(3-Aminopyridyl)carbonylamidosulfonyl]-2-phenylbenzoylmethionineExample 119A4-Aminosulfonyl-2-phenylbenzoylmethionine methyl ester

To a solution of 4-chlorosulfonyl-2-phenylbenzoyl methionine methyl ester from Example  
 5E in dichloromethane is added aqueous ammonia and the mixture is stirred until the  
 reaction is judged complete by TLC analysis. The organic phase is separated, dried and  
 5955 evaporated and the product is purified by chromatography on silica gel.

Example 119B4-Isocyanatosulfonyl-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant sulfonamide from Example 119A in chlorobenzene is treated with  
 5960 with oxalyl chloride according to the procedure of Franz et al. (*J. Org. Chem.*, 1964, 29,  
 2592) to give the title compound.

Example 119C4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine methyl ester

5965 A mixture of the resultant isocyanate from Example 119B (1 equivalent) in dichloromethane is treated with 3-aminopyridine (1 equivalent) and stirred until the reaction is judged complete by tlc analysis. The solvent is evaporated and the product is purified by chromatography on silica gel.

Example 119D4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

5970 The resultant compound from Example 119C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 120A-NH-CO-NH-SO<sub>2</sub>-B

5975 The anilines from Table 1 (B-NH<sub>2</sub>) are reacted according to the procedures of Example 5E to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5985 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 121A-NH-CO-NH-SO<sub>2</sub>-CH<sub>2</sub>-B

5990 The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 115A-C to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH<sub>2</sub>). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5995 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

6000 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 122

##### A-O-CH<sub>2</sub>-B

6005 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 27 with the exception that 3-hydroxypyridine is replaced by an alcohol from Table 6 (A-OH). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of  
6010 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the  
6015 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 123

##### A-O-CO-NH-B

6020 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-  
6025 butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which  
6030 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 124

##### A-O-CS-NH-B

6035

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>), (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 125

##### A-O-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 126

##### A-O-SO<sub>2</sub>-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH,



1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 127

##### A-O-CO-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 128

##### A-O-CS-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by

6110 removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which  
6115 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6120 Example 129

A-O-SO-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an  
6125 alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The  
6130 solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6135

Example 130

A-O-SO<sub>2</sub>-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an  
6140 alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring  
6145 the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane

and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the  
6150 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

### Example 131

6155

#### A-S-B

The anilines from Table 1 (B-NH<sub>2</sub>) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is  
6160 followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which  
6165 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6170

### Example 132

#### A-S-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis  
6175 step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica  
6180 gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the



anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6185

Example 133

A-S-CS-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>), (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6195

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6200

Example 134

A-S-SO-NH-B

6205

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6210

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6215

6220

Example 135A-S-SO<sub>2</sub>-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6230

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6235

Example 136A-S-CO-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6240

6245

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6250

Example 137A-S-CS-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the

6255

exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH) and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 138

##### A-S-SO-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 139

##### A-S-SO<sub>2</sub>-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of  
6295 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is  
complete. The solvent is evaporated and the residue is purified by chromatography on silica  
gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which  
case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the  
6300 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-  
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 140

6305 A-O-B

The procedure of Example 6 is used with the exception that 4-amino-2-phenylbenzoyl  
methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and 3-  
bromopyridine is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products  
derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by  
6310 removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant  
compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and  
trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is  
evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which  
6315 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the  
anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-  
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 141

6320 A-S-B

The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl  
methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and 2-  
chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-  
6325 I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is  
followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring  
the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane  
and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The  
solvent is evaporated and the residue is purified by chromatography on silica gel.

6330 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6335

#### Example 142

##### A-NH-B

The procedure of Example 24 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and 2-bromopyridine hydrobromide is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6340 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6350

#### Example 143

##### A-O-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 28 with the exception that 3-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6360 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 144A-S-CH<sub>2</sub>-B

6370

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I).

6375

For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6380

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6385

Example 145A-C≡C-B

The procedure of Example 47 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 4-

6390

bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6395

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6400

Example 146A-CH=CH-B

The products from Example 145 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 147

A-CH<sub>2</sub>-CH<sub>2</sub>-B

The products from Example 146 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 148

A-CO-C $\equiv$ C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 50 with the exception that 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-230 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 149

A-CO-CH=CH-B

The products from Example 148 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to

prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl,  
6440 butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 150

A-CO-CH<sub>2</sub>-CH<sub>2</sub>-B

The products from Example 149 are reacted according to the procedure of Example  
6445 49.

This example also encompasses compounds comprising a C-terminal ester moiety,  
in which case the final LiOH step is eliminated and the amino acid methyl esters used to  
prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl,  
butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6450

Example 151

A-SO<sub>2</sub>-B

The anilines from Table 1, entries 28-132 (B-NH<sub>2</sub>) are reacted according to the  
procedures of Example 13A. The resultant fluorides are reacted according to the procedure  
6455 of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from  
Table 7 (A-SH). The resultant sulfides are oxidized according to the procedure of Example  
14A. For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis  
step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by  
stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of  
6460 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is  
complete. The solvent is evaporated and the residue is purified by chromatography on silica  
gel.

This example also encompasses compounds comprising a C-terminal ester moiety,  
in which case the final LiOH step is eliminated and the amino acid methyl esters used to  
6465 prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl,  
butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 152

A-CH<sub>2</sub>SO<sub>2</sub>-B

The procedure of Example 12 is used with the exception that 4-amino-2-  
phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1, entries 28-  
132 (B-NH<sub>2</sub>) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table  
8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of  
Example 14A. For products derived from halides 202-239 from Table 8, the LiOH  
6475 hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting



group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6480 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

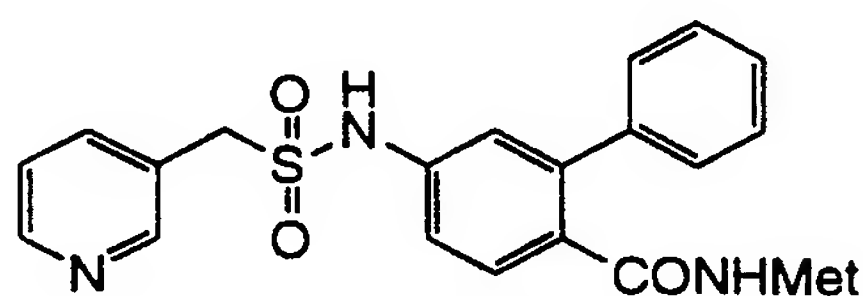
6485

### Example 153

#### A-SO<sub>2</sub>-CH<sub>2</sub>-B

The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of  
6490 Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of  
6495 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the  
6500 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



### Example 154

6505 {4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine

### Example 154A

{4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine methyl ester

A mixture of 3-chlorosulfonylmethylpyridine hydrochloride (1.0 equivalent) and (4-amino-2-phenylbenzoyl)methionine methyl ester (1.0 equivalent) in dichloromethane is treated with triethylamine (2.2 equivalents). When judged complete by TLC analysis, the reaction is diluted with ethyl acetate, and then is washed with pH 4 water, saturated NaHCO<sub>3</sub>, and brine. The mixture is dried and concentrated to give the crude title compound which is purified by chromatography on silica gel.

#### Example 154B

##### {4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine

The resultant compound from Example 154A is hydrolyzed according to the procedure of Example 1B to give the title product.

#### Example 155

##### A-CH<sub>2</sub>SO<sub>2</sub>-NH-B

The procedure of Example 154 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH<sub>2</sub>) and 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO<sub>2</sub>Cl).

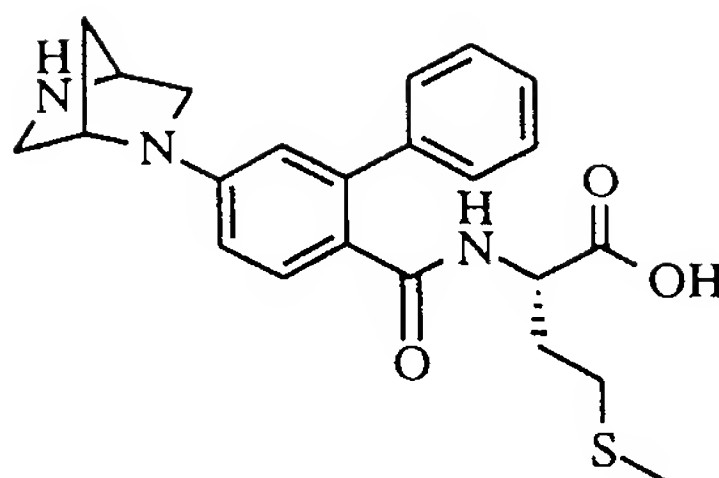
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

#### Example 156

##### A-SO<sub>2</sub>-NH-CH<sub>2</sub>-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 154 with the exception that 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO<sub>2</sub>Cl).

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

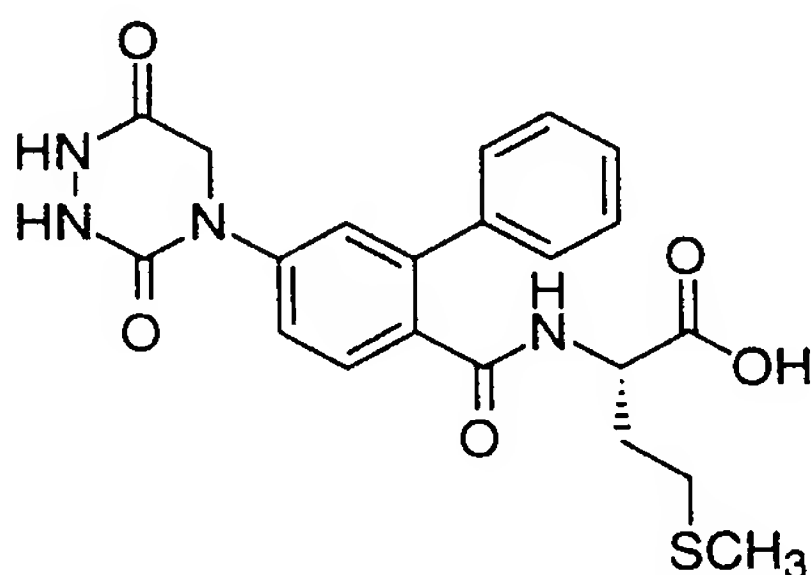


### Example 173

6545 [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine hydrochloride

To a solution of 74mg (0.13 mmol) of 2-phenyl-4-[(2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl]benzoylmethionine methyl ester, prepared as in Example 172A, in 5 ml of THF was added 0.4 ml (0.4 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 60 mg of the resulting free acid as a oily residue. To a 2 ml of a 1:1 solution of TFA and dichloromethane was added 60 mg of the acid. After 30 min, The reaction mixture was thoroughly evaporated in high vacuum to give an oily residue. The residue was triturated with 0.3 ml of 3 M anhydrous HCl-ether in 5 ml of ether and the white solid was collected by filtration to give 43 mg (66 %) of [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine hydrochloride: HPLC 95% (purity); <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.49-7.36 (m, 6H), 6.73 (dd, 1H, J=2.2, 8.4 Hz), 6.60 (d, 1H, J=2.1 Hz), 4.77 (s, 1H), 4.50 (m, 12H), 3.73 (m, 2H), 3.32 (m, 2H), 2.31-1.85 (m, 6H); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 175.0, 173.1, 148.5, 143.7, 142.4, 131.4, 129.9, 129.6, 128.8, 126.6, 115.5, 112.4, 59.7, 56.8, 53.6, 53.2, 51.8, 37.1, 31.9, 31.1, 15.8.

6565



Example 224[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine

6570

Example 224A(4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester

A mixture of (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8, 1.51 g, 4.21 mmol), glyoxylic acid monohydrate (466 mg, 5.06 mmol), sodium cyanoborohydride (1.0 M in THF, 4.2 mL), sodium acetate (0.5 g) and acetic acid (0.5 mL) in methanol (10 mL) was stirred for 14 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with saturated aqueous potassium dihydrogenphosphate, water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate, then 3% methanol-ethyl acetate) to give (4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester (1.46 g, 83%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.67 (d, 1H), 7.39 (m, 5H), 6.54 (dd, 1H), 6.45 (d, 1H), 5.96 (br d, 1H), 4.63 (m, 1H), 3.88 (d, 2H), 3.67 (s, 3H), 2.04 (m, 2H), 2.00 (s, 3H), 1.86 (m, 1H), 1.67 (m, 1H). MS (APCI<sup>+</sup>) m/e 417 (M+H)<sup>+</sup>.

Example 224B

6585 [4-(*N*-tert-butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester

A mixture of the (4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester prepared in Example 224A (1.04 g, 2.50 mmol), *tert*-butylcarbazate (661 mg, 5.0 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (489 mg, 3.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (576 mg, 3.0 mmol) in dichloromethane (10 mL) was stirred at room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate) to give [4-(*N*-  
6595 *tert*butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester (671 mg, 51%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.16 (d, 1H), 7.69 (d, 1H), 7.40 (m, 5H), 6.64 (dd, 1H), 6.53 (d, 1H), 6.45 (m, 1H), 5.96 (br d, 1H), 4.63 (m, 1H), 3.97 (d, 2H), 3.67 (s, 3H), 2.99 (m, 4H), 2.06 (m, 2H), 2.00 (s, 3H), 1.88 (m, 1H), 1.68 (m, 1H), 1.46 (s, 9H). MS (APCI<sup>+</sup>) m/e 531 (M+H)<sup>+</sup>.

6600

Example 224C[4-(N-tertbutoxycarbonylamino)carboxamidomethyl-(N-chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester

To a -78 °C solution of the [4-(N--tert-  
6605 butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester prepared in Example 224B (258 mg, 0.481 mmol) in dichloromethane (3 mL) was added phosgene (1.93 M in toluene, 0.38 mL, 0.74 mmol), followed by triethylamine (0.20 mL, 1.5 mmol). The reaction was then left to warm to ambient temperature over 14 hours. The reaction mixture was then filtered through silica gel (10 g), rinsed with ethyl acetate, and  
6610 concentrated *in vacuo*. The residue was purified by column chromatography (40% ethyl acetate-hexane) to give [4-(N-tertbutoxycarbonylamino)carboxamidomethyl-(N-chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester (171 mg, 60%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.24 (d, 1H), 7.33 (m, 5H), 7.28 (d, 1H), 6.68 (m, 3H), 4.39 (m, 2H), 4.30 (m, 1H), 3.62 (s, 3H), 2.25 (m, 2H), 2.00 (s, 3H), 1.83 (m, 2H), 1.51 (s,  
6615 9H).

Example 224D[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine methyl ester

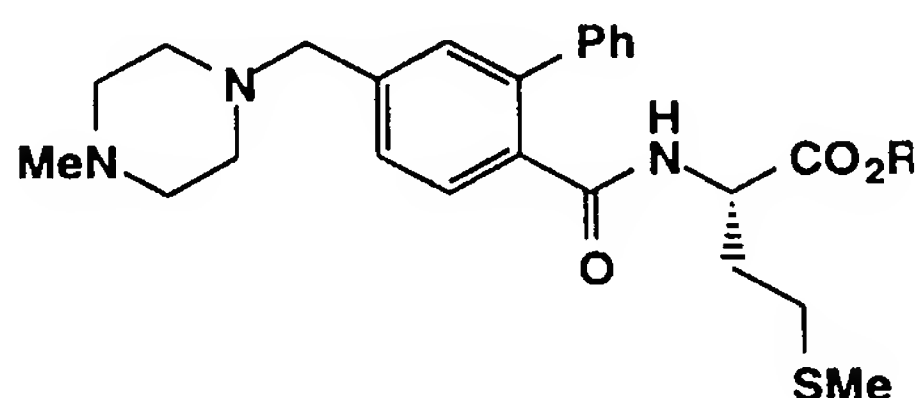
To a solution of the [4-(N-tertbutoxycarbonylamino)carboxamidomethyl-(N-  
6620 chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester prepared in Example 224C (70 mg, 0.118 mmol) in dichloromethane (2 mL) was added 2-mercaptoethanol (5 drops) and trifluoroacetic acid (1 mL). After 1.5 hour, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography (30% ethyl acetate-hexane) to give [4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine methyl ester (43 mg,  
6625 80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.86 (br s, 1H), 8.69 (d, 1H), 7.40 (m, 5H), 6.69 (dd, 1H), 6.56 (d, 1H), 5.76 (br d, 1H), 4.63 (m, 1H), 4.32 (s, 2H), 3.65 (s, 3H), 2.99 (m, 4H), 2.09 (t, 2H), 2.01 (s, 3H), 1.89 (m, 1H), 1.68 (m, 1H). MS (CI<sup>+</sup>) m/e 457 (M+H)<sup>+</sup>.

6630

Example 224E[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine



The desired compound was prepared by saponification of the product of Example 224D using the procedure of Example 211.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.32 (m, 5H), 7.23 (d, 1H), 6.79 (d, 1H), 6.63 (dd, 1H), 6.56 (d, 1H), 6.38 (m, 1H), 4.00 (m, 1H), 3.50 (s, 2 H), 2.07 (m, 2H), 1.97 (s, 3H), 1.79 (m, 2H). MS (APCI $^+$ )  $m/e$  465 (M+Na) $^+$ .



#### Example 289

#### [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine

#### Example 289A

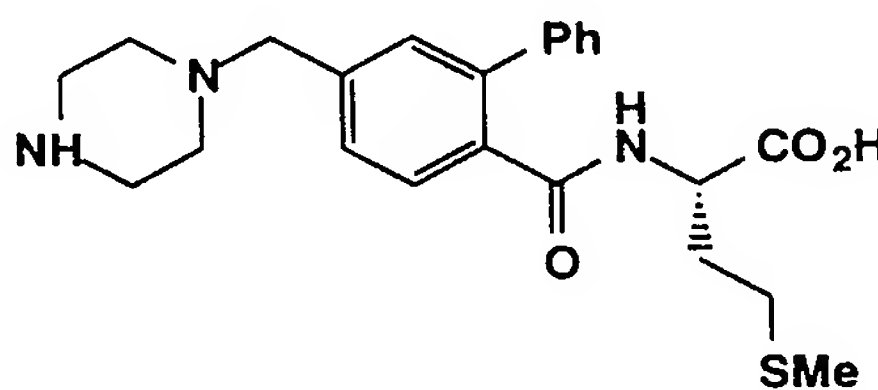
#### [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine methyl ester

A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, 1-methylpiperazine (0.607 g, 6.00 mmol),  $\text{K}_2\text{CO}_3$  (0.663 g, 4.80 mmol), KI (0.332 g, 2.00 mmol), and  $\text{Bu}_4\text{NBr}$  (0.032 g, 0.10 mmol) in DMF (5 mL) was stirred for 2 hours at ambient temperature and then concentrated under reduced pressure. The residue was treated with a saturated LiOH-methanol (10 mL) and then heated at reflux for 5 hours. The mixture was concentrated and the residue was dissolved in  $\text{H}_2\text{O}$ . This solution was extracted with ethyl acetate (5x), and the aqueous phase was then acidified by the addition of 3 M HCl and lyophilized. The resulting white foam was dissolved in DMF (20 mL) and the solution was treated with L-methionine, methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.33 g, 8.00 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.56 g, 8.00 mmol), and N-methylmorpholine (1.23 g, 12.0 mmol). The reaction mixture was stirred at ambient temperature for 20 hours, diluted with ethyl acetate, and extracted with a 2:1 mixture of  $\text{H}_2\text{O}$  and saturated aqueous  $\text{NaHCO}_3$  (2x), 1:1 mixture of the same (2x) and brine (2x). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated to provide a gold oil. Radial chromatography (30% methanol-ethyl acetate) afforded the desired compound (0.321 g, 35%).

Example 289[4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine

6665 Saponification of the product of Example 289A using the procedure of Example 287D gave the desired compound as a white foam as the bis-hydrochloride, mono-sodium chloride. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 1.76-1.95 (comp, 2H), 2.00 (s, 3H), 2.17-2.36 (comp, 2H), 2.52 (br, 3H), 3.18-3.80 (br, 8H), 4.28-4.60 (br, 3H), 7.30-7.42 (comp, 3H), 7.47-7.55 (comp, 3H), 7.67-7.73 (m, 1H), 7.74-7.80 (br, 1H), 8.63 (d, *J* = 7.8 Hz, 1H).

6670 LRMS (CI): 442 (M+H)<sup>+</sup>.

Example 290

6675 (4-piperazinylmethyl-2-phenylbenzoyl)methionine

Example 290A4-N-tert-butoxycarbonylpiperazinylmethyl-2-phenylbenzoic acid

6680 A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, piperazine (1.39 g, 16.0 mmol), K<sub>2</sub>CO<sub>3</sub> (0.663 g, 4.80 mmol), KI (0.332 g, 2.00 mmol), and Bu<sub>4</sub>NBr (0.032 g, 0.10 mmol) in DMF (7 mL) was stirred for 2 hours at ambient temperature and then concentrated under reduced pressure. The residue was treated with saturated LiOH-methanol (10 mL) and then heated at reflux for 5 hours. The mixture was concentrated and the residue was dissolved in H<sub>2</sub>O.

6685 This solution was extracted with ethyl acetate (5x), and the aqueous phase was then acidified by the addition of 3 M HCl and lyophilized. The resulting white foam was dissolved in a 1:1 mixture of H<sub>2</sub>O and 0.979 M NaOH (86 mL), and the solution was treated with *di-tert*-butyldicarbonate (6.68 g, 30.0 mmol). The reaction mixture was stirred at ambient temperature for 15 hours and then concentrated to remove THF. The mixture

6690 was treated with H<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub> and then extracted with an ether (4x).

The aqueous phase was acidified to pH 3 by the addition of 3 M HCl and then extracted with 4:1 CHCl<sub>3</sub>-methanol (10x). The combined organic extracts were dried twice with saturated aqueous Na<sub>2</sub>SO<sub>4</sub> and concentrated to provide the desired compound (0.544 g, 69%) as an amber wax.

6695

### Example 290B

#### (4-*N*-tert-butoxycarbonylpiperazinylmethyl-2-phenylbenzoyl)methionine methyl ester

A solution of the product of Example 290A (0.544 g, 1.37 mmol), L-methionine, methyl ester hydrochloride (0.553 g, 2.74 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (1.14 g, 6.85 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.34 g, 6.85 mmol), and *N*-methylmorpholine (0.980 g, 9.59 mmol) in DMF (14 mL) was stirred at ambient temperature for 16 hours. The mixture was diluted with ethyl acetate and then extracted with a 2:1 mixture of H<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub> (2x), a 1:1 mixture of the same (2x) and brine (2x). The organic phase was dried (MgSO<sub>4</sub>) and concentrated to provide an amber oil. Radial chromatography (1:1 hexane-ethyl acetate) afforded the desired compound (0.356 g, 48%) as an amber oil.

6700

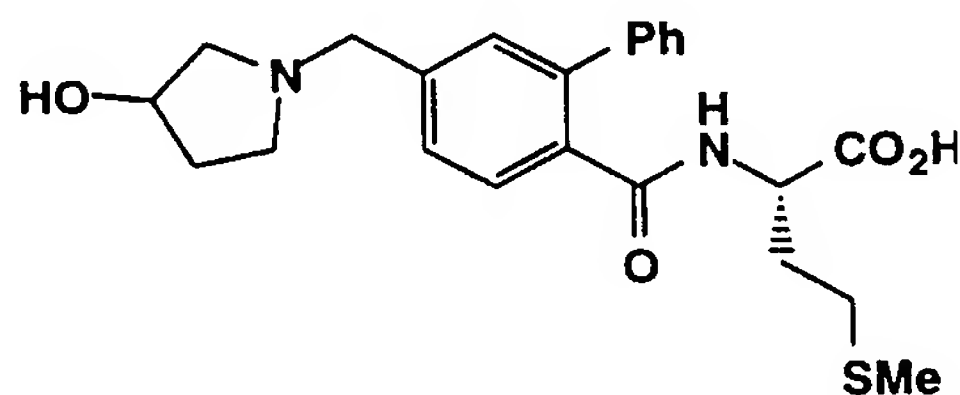
6705

### Example 290C

#### (4-piperazinylmethyl-2-phenylbenzoyl)methionine

The desired compound was prepared from the product of Example 290B according to the method of Example 286E. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.75-1.96 (comp, 2H), 2.00 (s, 3H), 2.17-2.35 (comp, 2H), 3.3-3.7 (br, 8H), 4.28-4.38 (m, 1H), 4.28-4.38 (m, 1H), 4.38-4.54 (br, 2H), 7.30-7.44 (comp, 3H), 7.46-7.56 (comp, 3H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.76-7.82 (br, 1H), 8.66 (d, *J* = 7.7 Hz, 1H), 9.86-10.06 (br, 1H), 12.30-12.70 (br, 1H). LRMS (CI) *m/e* 248 (M+H)<sup>+</sup>.

6715



### Example 291



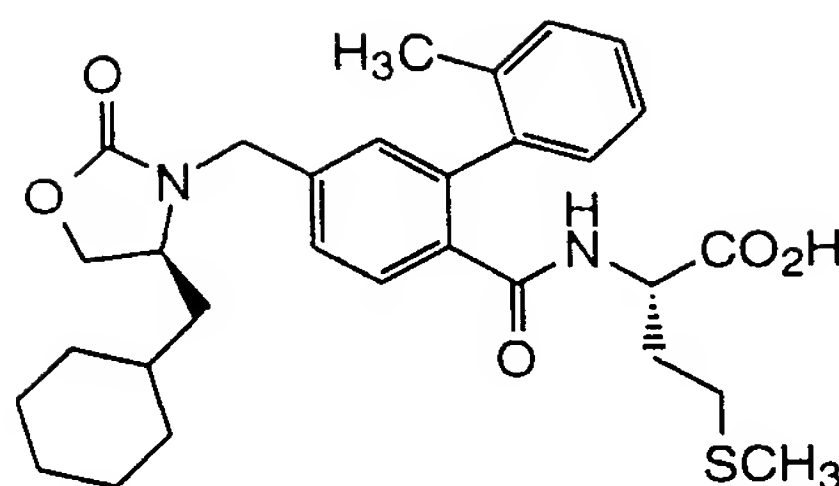
6720

[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionineExample 291A[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine methyl ester

A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, 3-pyrrolidinol (0.178 g, 2.00 mmol), K<sub>2</sub>CO<sub>3</sub> (0.553 g, 4.00 mmol), and Bu<sub>4</sub>NI (0.0754 g, 0.20 mmol) in CH<sub>3</sub>CN (5 mL) was stirred for 15 hours, treated with LiOH•H<sub>2</sub>O (0.506 g, 12.0 mmol), and then heated at reflux for 5 hours. The solution was cooled to ambient temperature and added to a mixture of L-methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (1.66 g, 10.00 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.96 g, 10.00 mmol), and triethylamine hydrochloride (2.81 g, 20 mmol) in CH<sub>3</sub>CN (15 mL). After 12 days the mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The solution was extracted with a 1:1 mixture of H<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub> (4x) and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to provide a gold oil. Radial chromatography (12% methanol-ethyl acetate) afforded the desired compound (0.494 g, 56%).

Example 291B[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine

Saponification of the product of Example 289A using the procedure of Example 287D gave the desired compound as a white foam as the bis-hydrochloride, mono-sodium chloride. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.77-2.06 (comp, 5H), 2.16-2.36 (comp, 2H), 2.94-3.04 (m, 1H), 3.12-3.34 (comp, 2H), 3.34-3.56 (comp, 2H), 4.28-4.37 (m, 1H), 4.37-4.60 (comp, 2H), 4.60-5.50 (br, 2H), 7.32-7.43 (comp, 3H), 7.45-7.56 (comp, 3H), 7.65-7.80 (comp, 2H), 8.68 (d, *J* = 7.8 Hz, 1H), 11.2-11.9 (m, 1H). LRMS (CI) *m/e* 429 (M+H)<sup>+</sup>.

Example 349

[4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Example 349A

[4-(1-hydroxy-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

6755 A mixture of [4-formyl-2-(2-methylphenyl)benzoyl]methionine ethyl ester (614 mg, 1.54 mmol), prepared according to Example 158F except substituting [4-hydroxymethyl-2-(2-methylphenyl)benzoic acid for 4-hydroxymethyl-2-phenylbenzoic acid in Example 158E, (S)-(+)-2-amino-3-cyclohexyl-1-propanol hydrochloride (357 mg, 1.84 mmol) and diisopropylethylamine (0.135 mL, 0.77 mmol) in toluene was refluxed for 5 hours using a

6760 Dean-Stark apparatus. The reaction mixture was cooled to ambient temperature and diluted with ethanol. Sodium cyanoborohydride (145 mg) and o-bromocresol green was added. The reaction mixture was stirred while acidity was maintained using HCl-ethanol. The reaction was quenched with saturated aqueous potassium carbonate and the mixture was extracted with dichloromethane (2x). The combined organic layers were dried over

6765 magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (5% methanol-chloroform) gave the desired compound (840 mg).

Example 349B

[4-(1-hydroxy-3-cyclohexylprop-2-yl-N-ethoxycarbonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

6770

To a solution in THF of the product of Example 348A (173 mg, 0.32 mmol) and diisopropylethylamine (66  $\mu$ L, 0.38 mmol) was added ethyl chloroformate (40  $\mu$ L, 0.38 mmol) and the reaction mixture was stirred for 1.5 hours at ambient temperature. The reaction mixture was poured into ethyl acetate and the organic phase was washed with

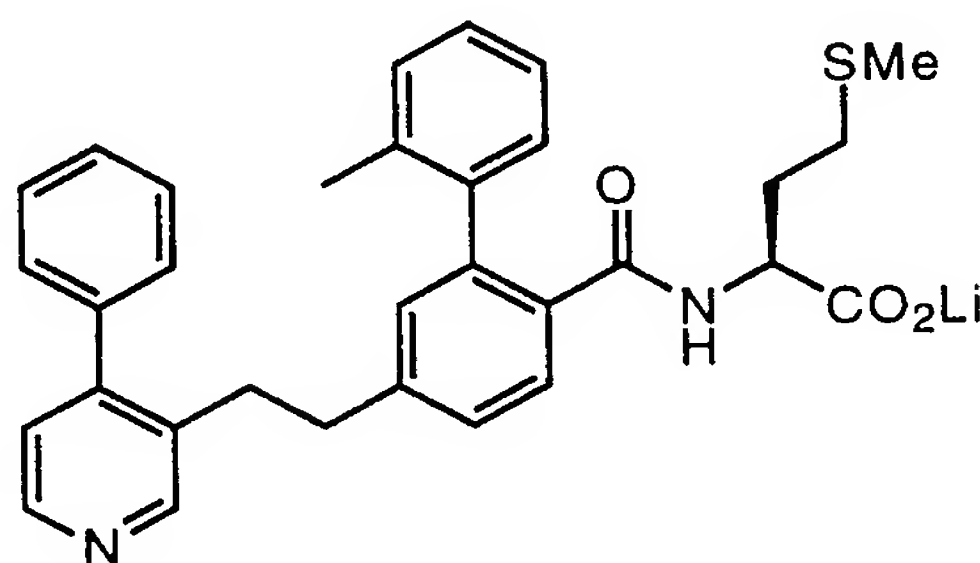
6775 aqueous 2N HCl, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the desired compound as a clear oil which was used without further purification.

Example 349C[4-(5-cyclohexylmethyl-2-oxazolidon-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

6780 To a 100 °C solution of the product of Example 348B in toluene was added sodium ethoxide (21% in ethanol, 30  $\mu$ L) and the reaction mixture was stirred for 10 minutes. The reaction mixture was cooled to ambient temperature and diluted with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on

6785 silica gel (33% ethyl acetate-hexane) gave the title compound as the ethyl ester. Saponification of the ethyl ester using lithium hydroxide gave the title compound.  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  8.13 (m, 1H), 7.41 (d,  $J$ = 7 Hz, 1H), 7.25 (d,  $J$ = 7 Hz, 1H), 7.11-7.02 (m, 4H), 4.45 (d,  $J$ = 15 Hz, 1H), 4.34 (dd,  $J$ = 9, 8 Hz, 1H), 4.19 (d,  $J$ = 15 Hz, 1H), 4.10 (m, 1H), 3.84 (dd,  $J$ = 8, 8 Hz, 1H), 3.58 (m, 1H), 2.10-1.83 (m, 5H),

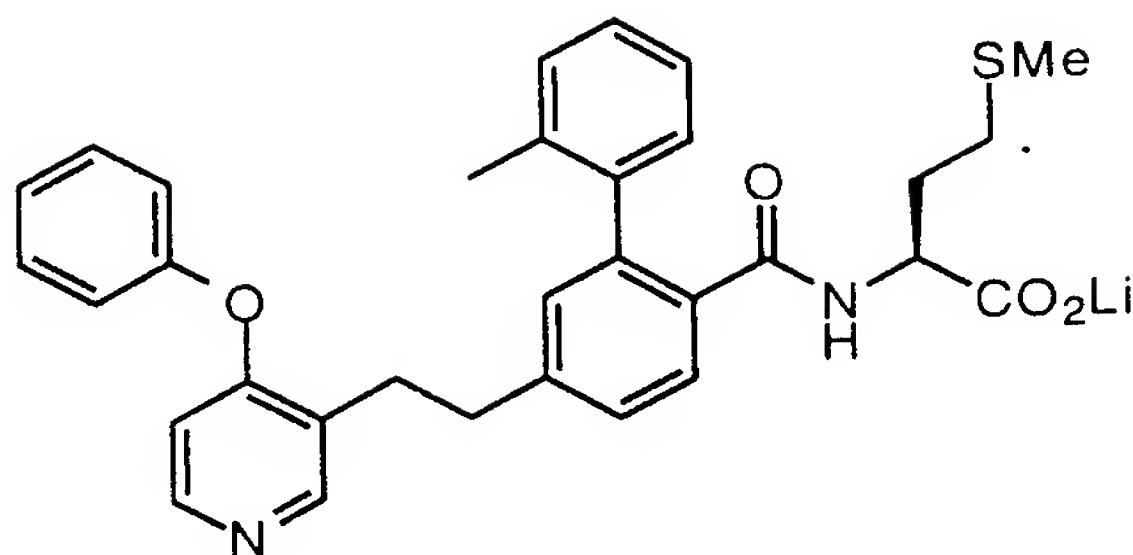
6790 1.85 (s, 3H), 1.47-1.37 (m, 8H), 1.10-0.92 (m, 5H), 0.85-0.57 (m, 2H). MS (DCI- $\text{NH}_3$ )  $m/e$  539 ( $\text{M}+\text{H}$ ) $^+$ , 556 ( $\text{M}+\text{NH}_4$ ) $^+$ .

Example 452N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

6795 The desired compound was prepared according to the method of Examples 210 - 212

$^1\text{H}$  nmr (300 MHz, DMSO- $d_6$ ):  $\delta$  7.2-7.04 (m, 15 H), 6.89 (dd, 1 H), 6.54 (br d, 1 H), 4.12 (m, 1 H), 2.81 (t, 2 H), 2.63 (t, 2 H), 2.00 (m, 1 H), 1.88-1.87 (br s, 6 H), 1.73 (m,

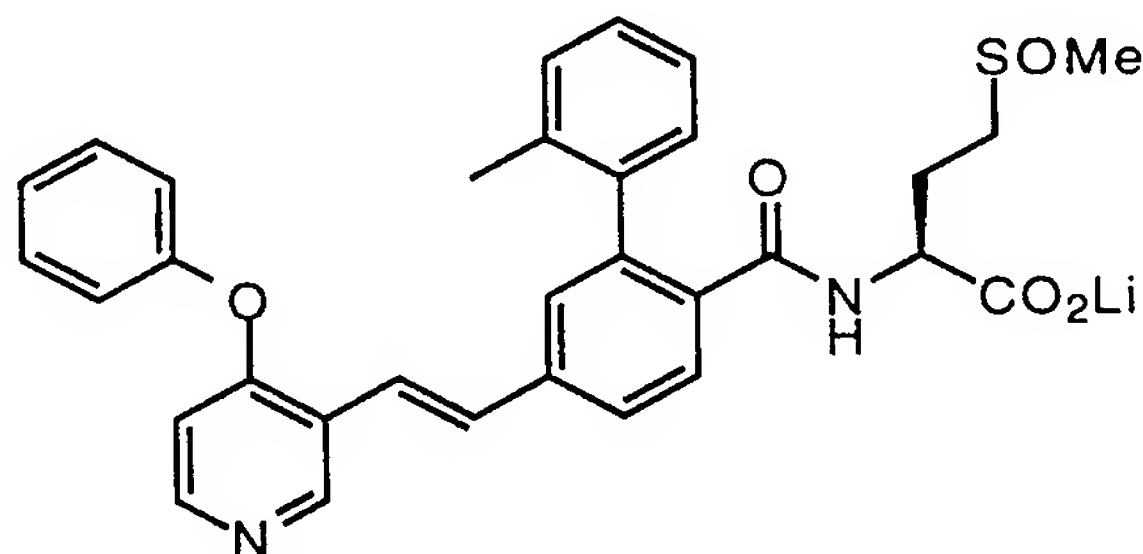
6800 2 H), 1.56 (m, 1 H). MS (ESI  $-$ ):  $m/e$  522 ( $\text{M}-\text{H}$ ) $^-$ .

Example 453

6805 N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.88 (br d, 1 H), 7.55 (m, 2 H), 7.40-7.17 (m, 11 H), 7.10 (t, 1 H), 6.96 (m, 4 H), 3.65 (m, 1 H), 2.15 (m, 1 H), 2.00 (m, 1 H), 1.91 (br s, 6 H), 1.75-1.55 (m, 2 H). MS (APCI -): m/e 536 (M-H)<sup>-</sup>.

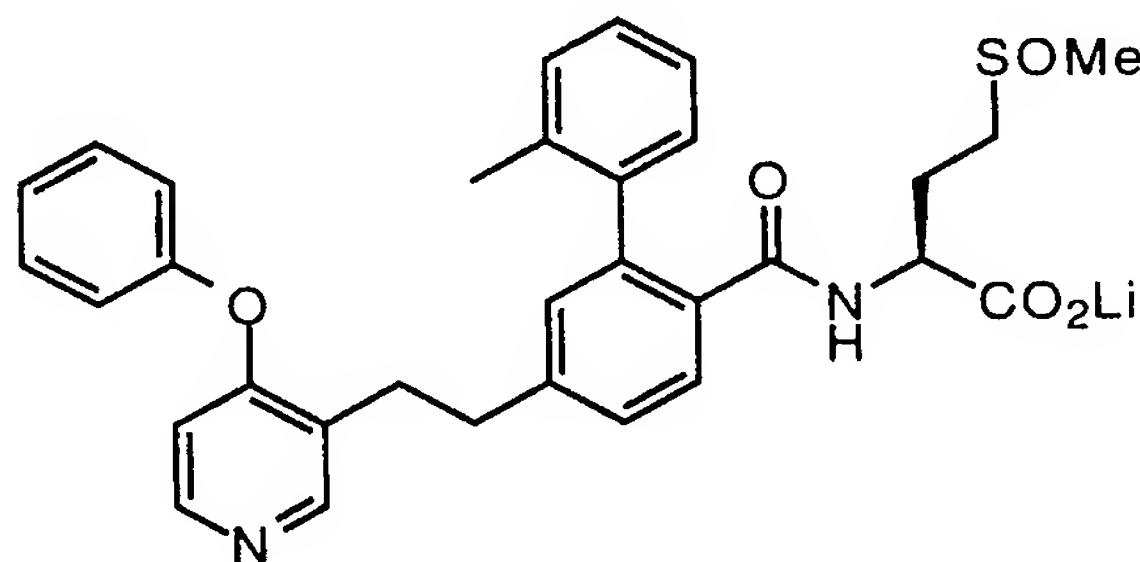
6810

Example 454

6815 N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfanylbutanoic acid lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.88 (br d, 1 H), 7.62-7.50 (m, 2 H), 7.40-7.17 (m, 11 H), 7.10 (t, 1 H), 6.98 (m, 4 H), 3.90 (m, 1 H), 2.45 (s, 3 H), 2.39, 2.36 (2 s's, 3 H), 2.10-1.64 (m, 4 H). MS (ESI -): m/e 552 (M-H)<sup>-</sup>.

6820

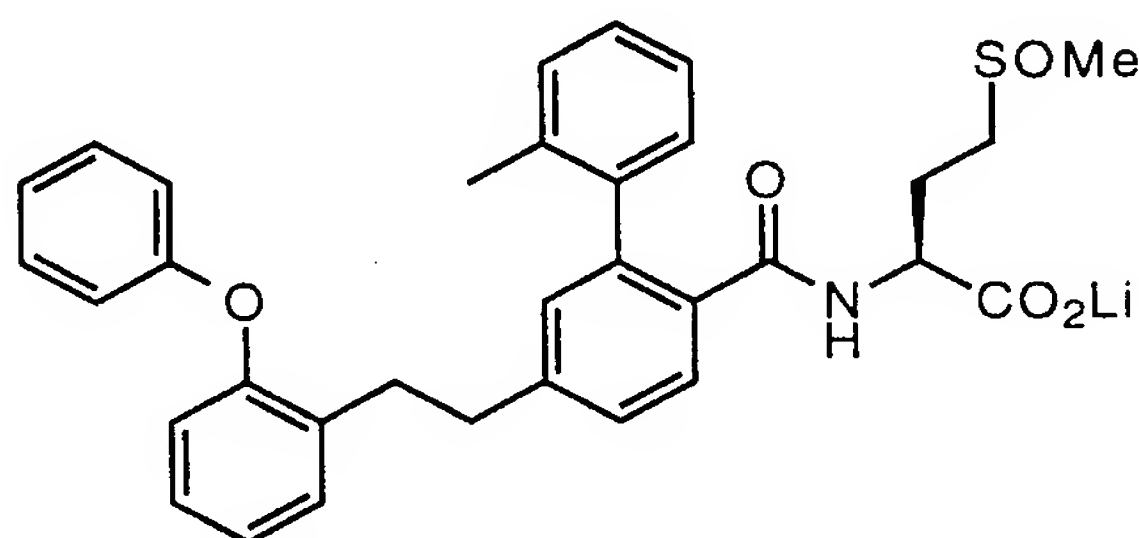


Example 455N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

6825

The desired compound was prepared according to the method of Examples 210 - 212.  $^1\text{H}$  nmr (300 MHz, DMSO- $d_6$ ):  $\delta$  7.45-6.90 (m, 17 H), 3.65 (m, 1 H), 2.88 (br s, 4 H), 2.18-2.00 (m, 2 H), 1.91 (br s, 6 H), 1.70-1.50 (m, 2 H). MS (APCI  $-$ ):  $m/e$  538 ( $M-H$ ) $^-$ .

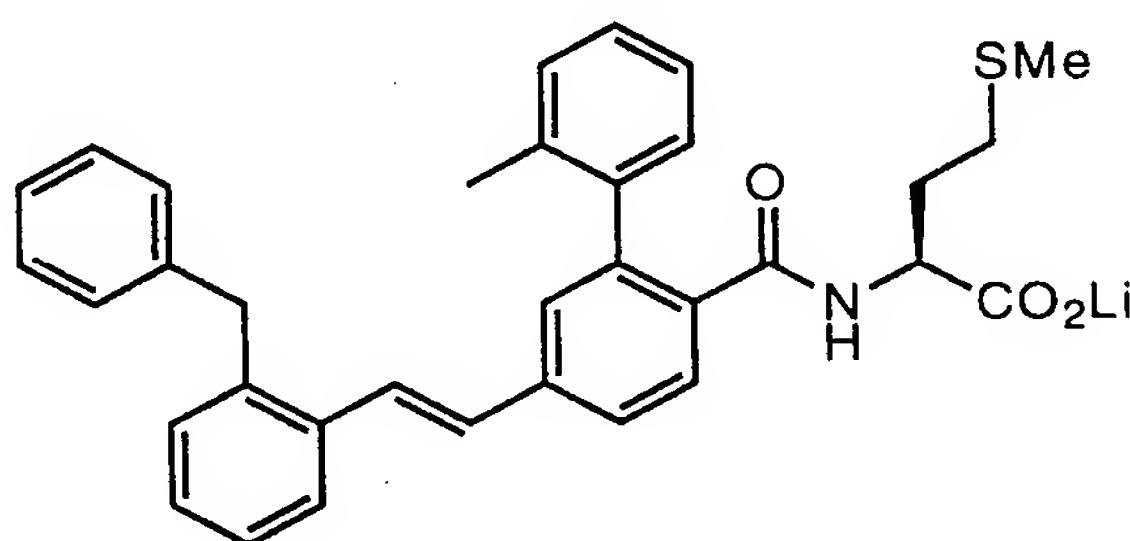
6830

Example 456N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

6835

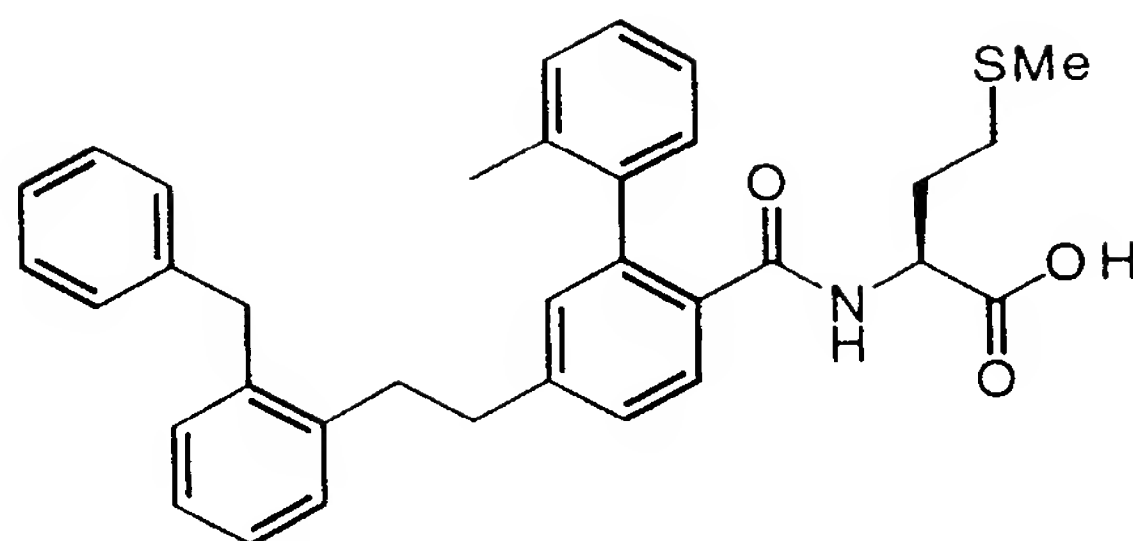
The desired compound was prepared according to the method of Examples 210 - 212.  $^1\text{H}$  nmr (300 MHz, DMSO- $d_6$ ):  $\delta$  7.43 (m, 1 H), 7.34 (m, 3 H), 7.25-7.00 (m, 9 H), 6.95 (m, 1 H), 6.85 (m, 3 H), 3.90 (m, 1 H), 2.88 (br s, 4 H), 2.41-2.37 (4 s's, 6 H), 2.10-1.64 (m, 4 H). MS (ESI  $-$ ):  $m/e$  554 ( $M-H$ ) $^-$ .

6840

Example 457N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

6845

The desired compound was prepared according to the method of Examples 210 and 211.  $^1\text{H}$  nmr (300 MHz, DMSO- $d_6$ ):  $\delta$  7.70 (m, 1 H), 7.59 (m, 1 H), 7.51 (m, 2 H), 7.34-7.10 (m, 14 H), 6.96 (br s, 1 H), 4.17 (br s, 2 H), 3.63 (m, 1 H), 2.19 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI  $-$ ):  $m/e$  534 ( $M-H$ ) $^-$ .

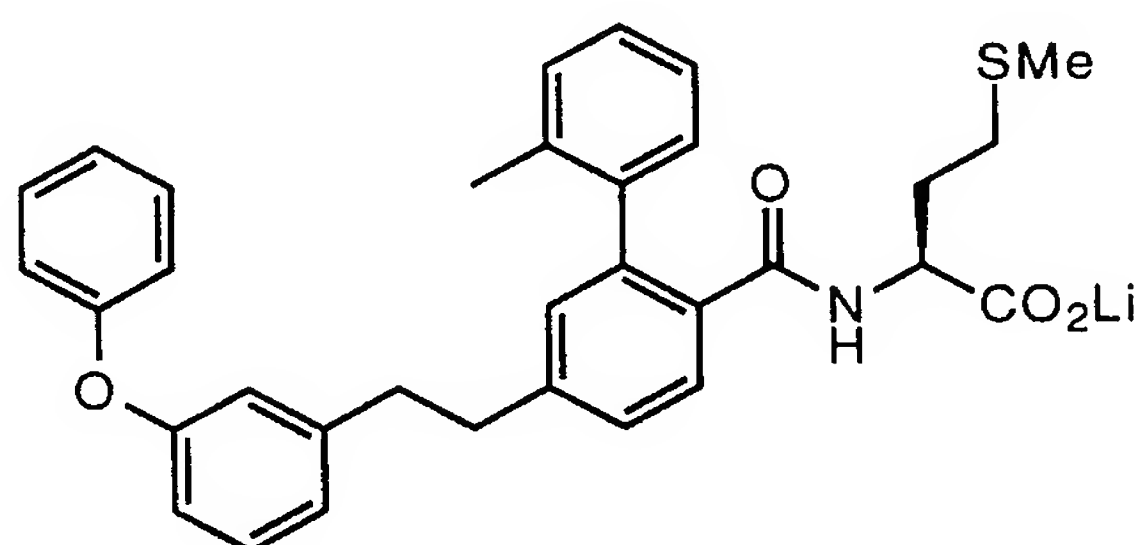


6850

Example 458N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.60-7.40 (m, 3 H), 7.25-7.07 (m, 12 H), 7.00-6.80 (m, 2 H), 3.97 (s, 2 H), 3.61 (m, 1 H), 2.83 (m, 2 H), 2.72 (m, 2 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.96,1.91(2 br s's, 6 H), 1.80-1.52 (m, 2 H). MS (APCI -): m/e 536 (M-H)<sup>-</sup>.

6855

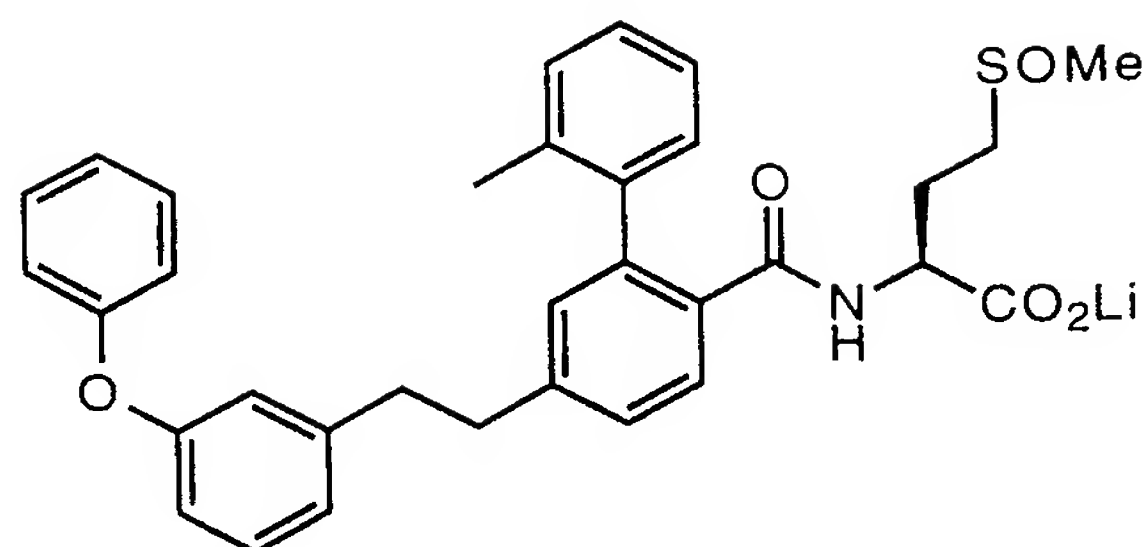


6860

Example 459N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.44 (d, 1 H), 7.35 (tt, 2 H), 7.25 (dt, 1H), 7.19 (m, 4 H), 7.10 (tt, 2 H), 6.98 (dt, 1 H), 6.96-6.83 (m, 5 H), 6.79 (ddd, 1 H), 3.64 (m, 1 H), 2.91 (br s, 4 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 538 (M-H)<sup>-</sup>.

6865



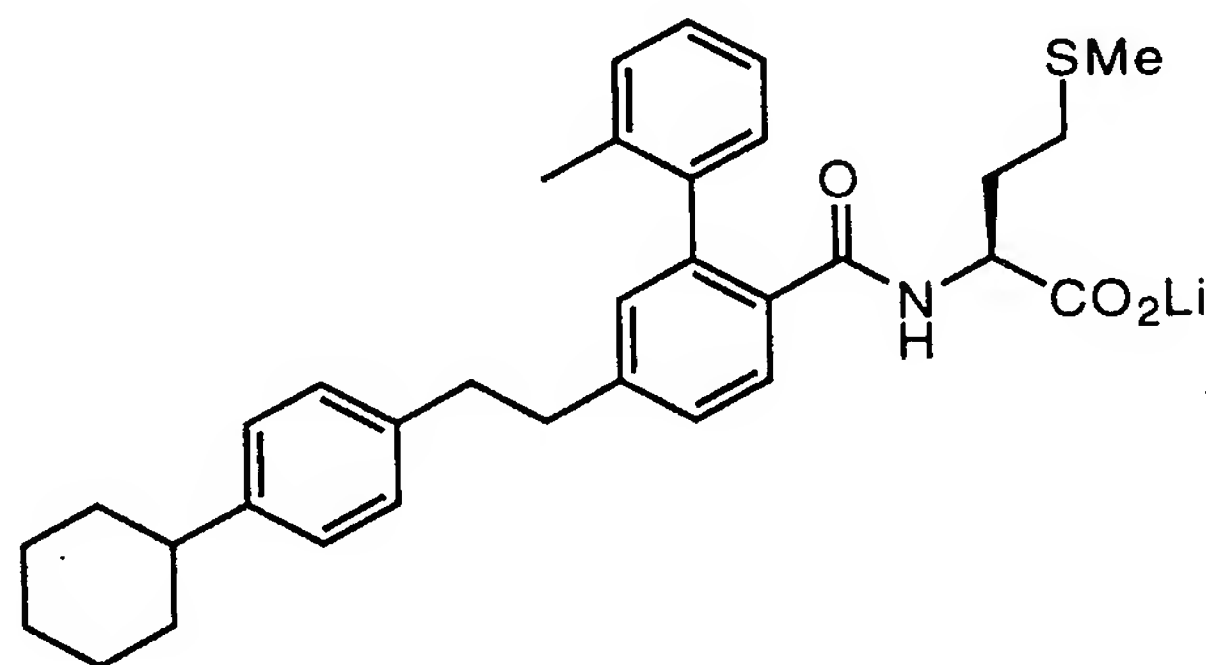
6870

Example 460N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

The desired compound was prepared according to the method of Examples 210 -

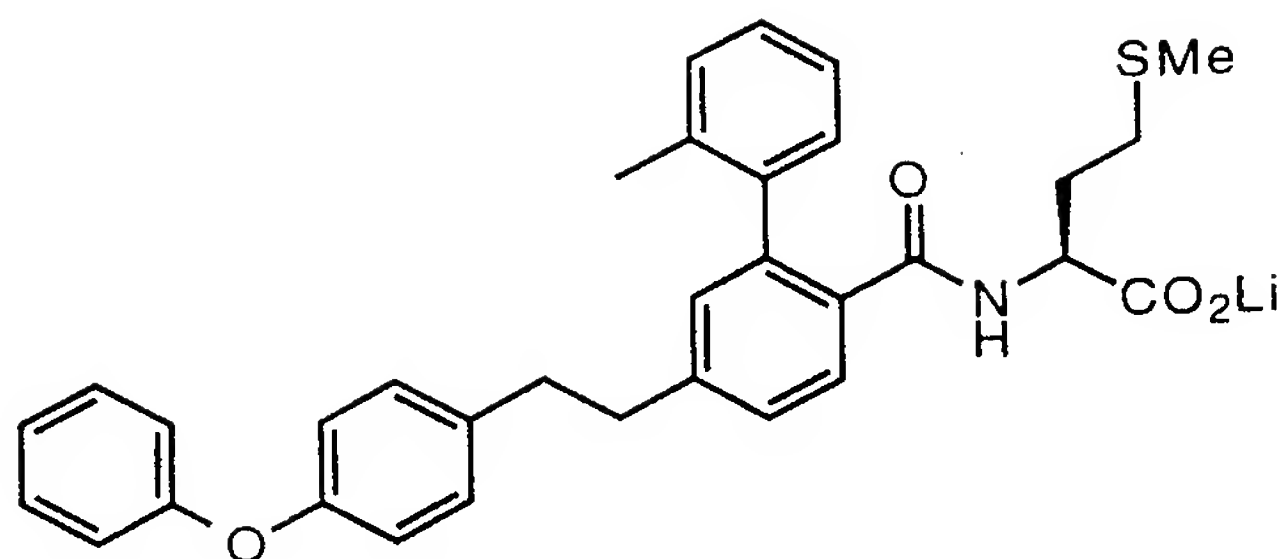
6875 212.. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): 7.44 (dd, 1 H), 7.35 (tt, 2 H), 7.25 (dt, 1 H), 7.19 (m, 4 H), 7.10 (tt, 2 H), 6.98 (dt, 1 H), 6.96-6.83 (m, 5 H), 6.79 (ddd, 1 H), 3.90 (m, 1 H), 2.91 (br s, 4 H), 2.45 (s, 3 H), 2.39, 2.36 (2 s's, 3 H), 2.20-1.54 (m, 4 H). MS (ESI -): m/e 554 (M-H)<sup>-</sup>.

6880

Example 461N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

6885 212.. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.45 (d, 1 H), 7.29 (dd, 1 H), 7.25-7.05 (m, 8 H), 6.88 (m, 2 H), 3.64 (m, 1 H), 2.88 (m, 4 H), 2.44 (m, 1 H), 2.10-1.30 (m, 14 H), 1.91 (br s, 6 H). MS (APCI -): m/e 528 (M-H)<sup>-</sup>.

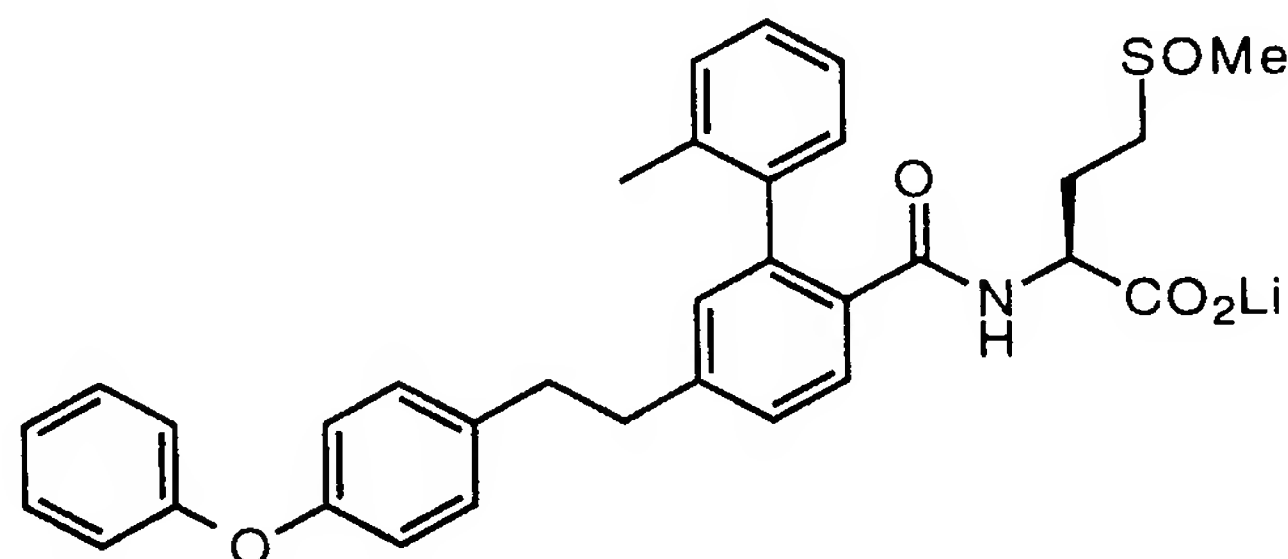


6890

Example 462N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

212..<sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): 7.45 (d, 1 H), 7.40-7.27 (m, 3 H), 7.25-7.12 (m, 7  
 6895 H), 7.10 (tt, 1 H), 6.98-6.87 (m, 5 H), δ 3.67 (m, 1 H), 2.91 (br s, 4 H), 2.16-1.95 (m, 2  
 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 538 (M-H)<sup>-</sup>.



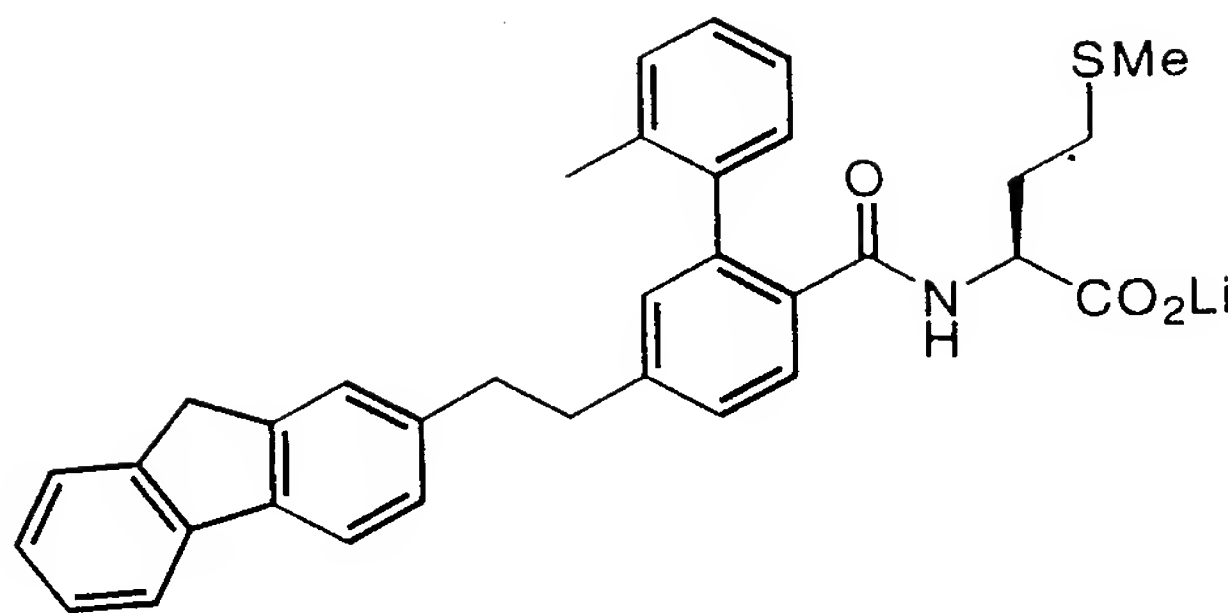
6900

Example 463N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

The desired compound was prepared according to the method of Examples 210 -

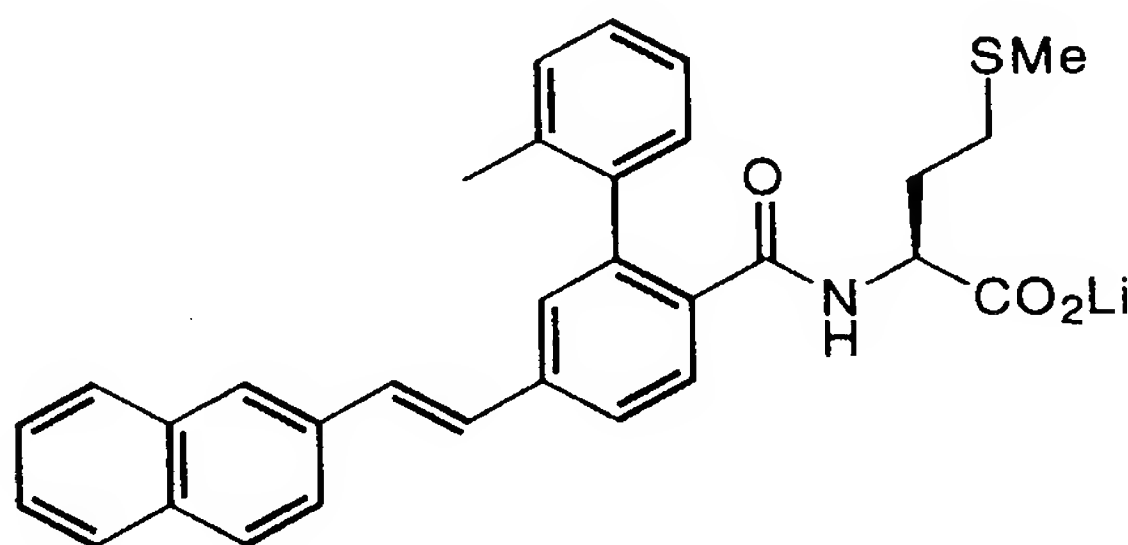
212..<sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): 7.66-6.87 (m, 17 H), 3.70 (m, 1 H), 2.92 (br s, 4 H),  
 6905 2.40-2.37 (4 s's, 6 H), 2.20-1.54 (m, 4 H). MS (ESI -): m/e 554 (M-H)<sup>-</sup>.



Example 464

6910 N-[4-(2-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

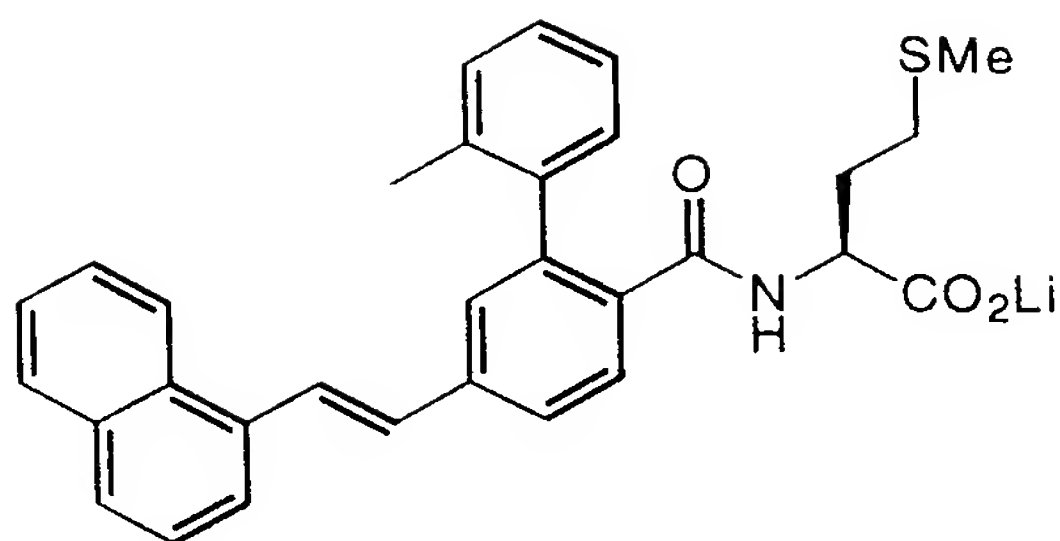
The desired compound was prepared according to the method of Examples 210 - 212. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.84 (d, 1 H), 7.77 9d, 1 H), 7.56 (d, 1 H), 7.45 (d, 1 H), 7.44 (s, 1 H), 7.40-6.86 (m, 10 H), 3.86 (s, 2 H), 3.64 (m, 1 H), 2.98 (br s, 4 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 538 (M-H)<sup>-</sup>.

Example 465

6920 N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine

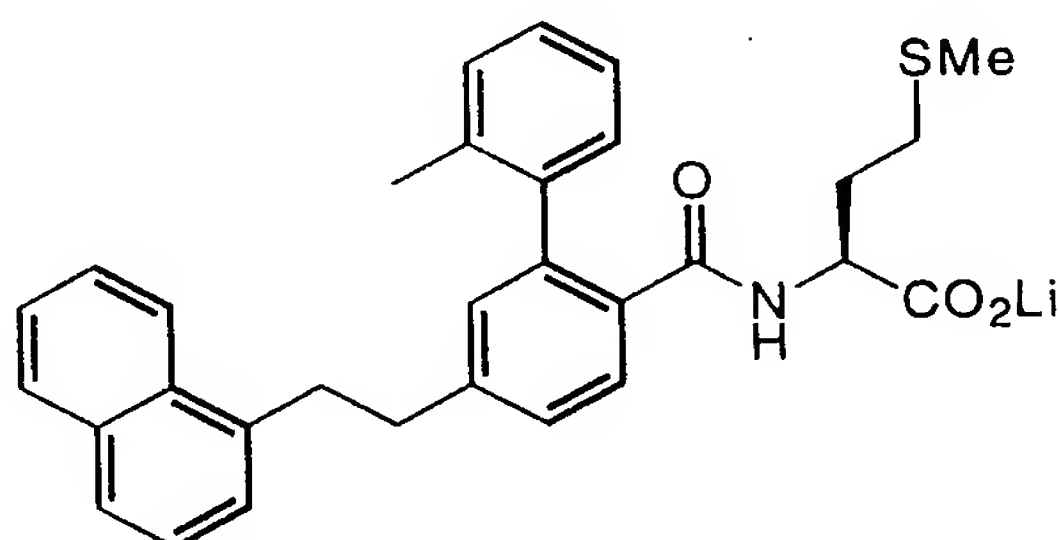
The desired compound was prepared according to the method of Examples 210 and 211. <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub>): δ: δ 8.07 (dd, 1 H), 7.90-7.80 (m, 4 H), 7.74 (dd, 1 H), 7.66 (dd, 1 H), 7.51 (m, 2 H), 7.42-7.31 (m, 6 H), 7.25 (m, 1 H), 5.94 (t, 1 H), 4.60 (m, 1 H), 2.20-2.00 (4 s's, 6 H), 2.12 (m, 1 H), 2.03 (m, 1 H), 1.94 (m, 1 H), 1.58 (m, 1 H). MS (CI +): m/e 496 (M+H)<sup>+</sup>.

6925

Example 466

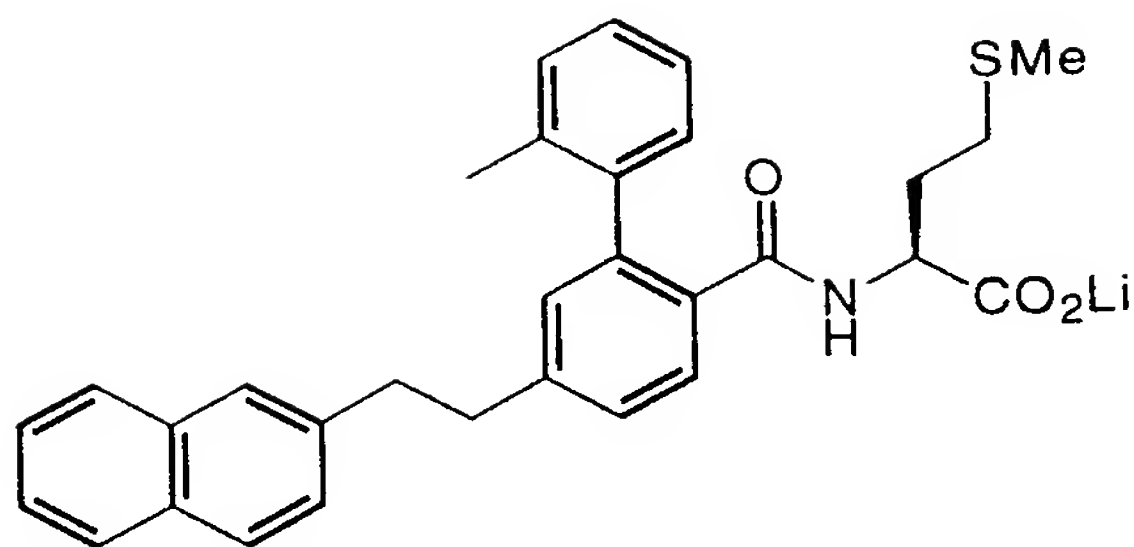
6930 N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. <sup>1</sup>H nmr (300 MHz, MeOD-d<sub>4</sub>): δ 8.28 (d, 1 H), 8.12 (dd, 1 H), 7.90-7.72 (m, 5 H), 7.63-7.42 (m, 5 H), 7.35-7.10 (m, 5 H), 4.25 (m, 1 H), 2.98 (br s, 4 H), 2.30 (m, 1 H), 2.10 (m, 1 H), 2.02-1.97 (4 s's, 6 H), 1.84 (m, 1 H), 1.68 (m, 1 H). MS (ESI -): m/e 494 (M-H)<sup>-</sup>.

Example 467

6940 N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

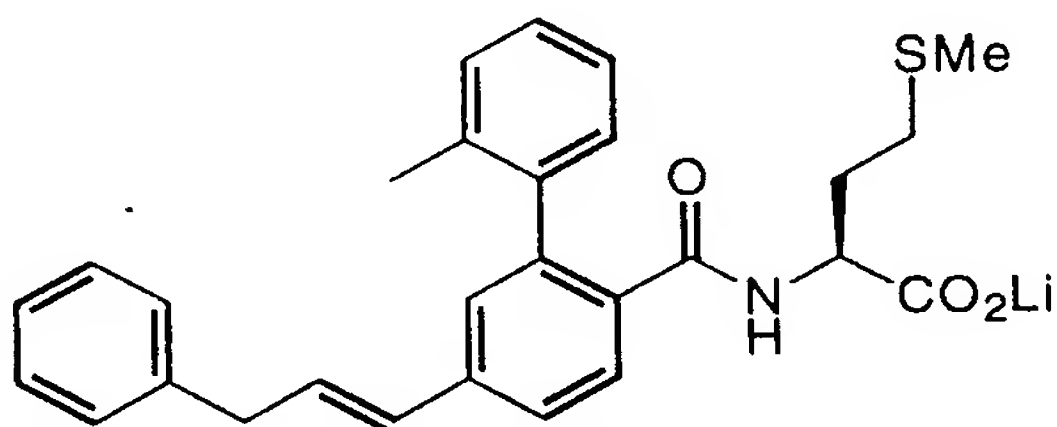
The desired compound was prepared according to the method of Examples 210 - 212. <sup>1</sup>H nmr (300 MHz, MeOD-d<sub>4</sub>): δ 8.08 (d, 1 H), 7.85 (dd, 1 H), 7.70 (d, 1 H), 7.63-7.38 (m, 4 H), 7.37-7.15 (m, 6 H), 7.05-6.83 (m, 2 H), 4.24 (m, 1 H), 3.42 (t, 2 H), 3.12 (t, 2 H), 2.27-2.05 (m, 2 H), 2.00 (br s, 6 H), 1.90-1.60 (m, 2 H). MS (ESI -): m/e 496 (M-H)<sup>-</sup>.

Example 468

6950 N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. <sup>1</sup>H nmr (300 MHz, MeOD-d<sub>4</sub>): δ 7.66 (m, 3 H), 7.45 (m, 2 H), 7.31 (m, 2 H), 7.24 (dd, 1 H), 7.20 (dd, 1 H), 7.13-7.00 (m, 4 H), 6.80 (br d, 1 H), 4.13 (m, 1 H), 3.01 (t, 4 H), 1.91, 1.88, 1.81 (3 br s's, 6 H), 1.95-1.48 (m, 4 H). MS (ESI -): m/e 496 (M-H)<sup>-</sup>.

6955

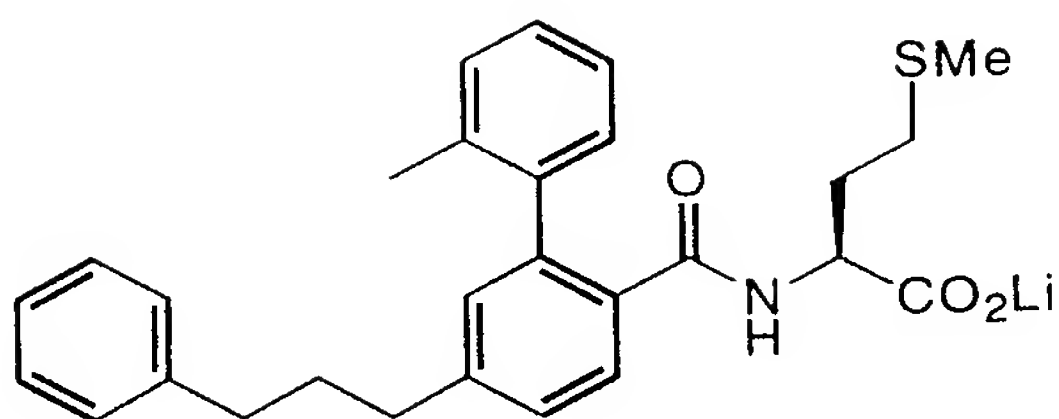
Example 469

N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine  
(1:1 mixture of olefin isomers)

6960

The desired compound was prepared according to the method of Examples 210 and 211. <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub>): δ 8.00, 7.96 (2 d's, from each of the isomers, 1 H), 7.48-7.08 (11 H), 6.52-6.30 (m, 2 H), 5.88 (m, 1 H), 4.56 (m, 1 H), 3.60 (2 d's, from each of the isomers, 2 H), 2.20-2.00 (m, 8 H), 1.90 (M, 1 H), 1.52 (m, 1 H). MS (CI +) m/e 460 (M+H)<sup>+</sup>.

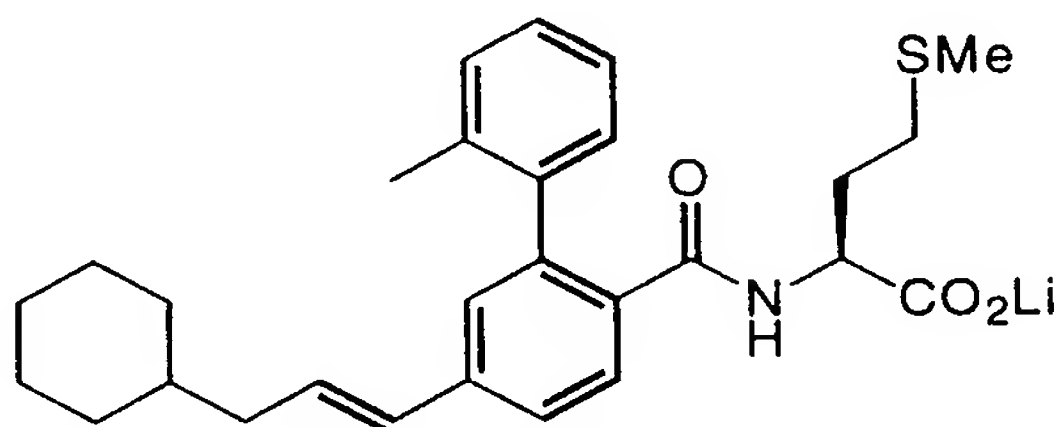
6965

Example 470

6970 N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.. <sup>1</sup>H nmr (300 MHz, MeOD-d<sub>4</sub>): δ 7.68 (t, 1 H), 7.65 (t, 1 H), 7.51 (m, 2 H), 7.34-7.06 (m, 9 H), 6.93 (m, 1 H), 4.17 (m, 1 H), 2.73 (t, 2 H), 2.66 (t, 2 H), 1.96 (m, 1 H), 1.99 (m, 3 H), 1.97, 1.89 (2 br s's, 6 H), 1.72 (m, 1 H), 1.53 (m, 1 H). MS (ESI -): m/e 510 (M-H)<sup>-</sup>.

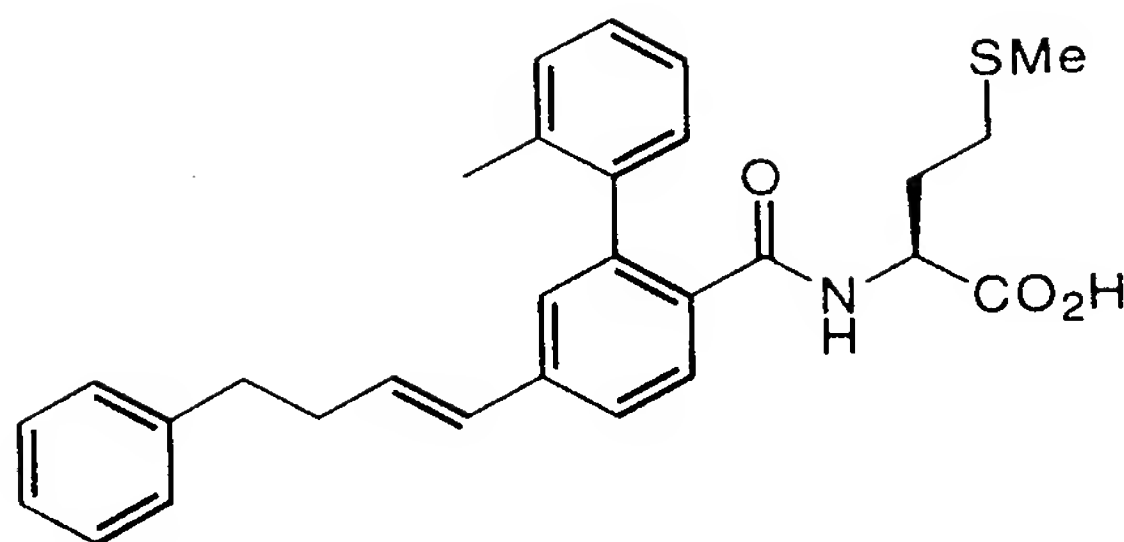
6975

Example 471

6980 N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

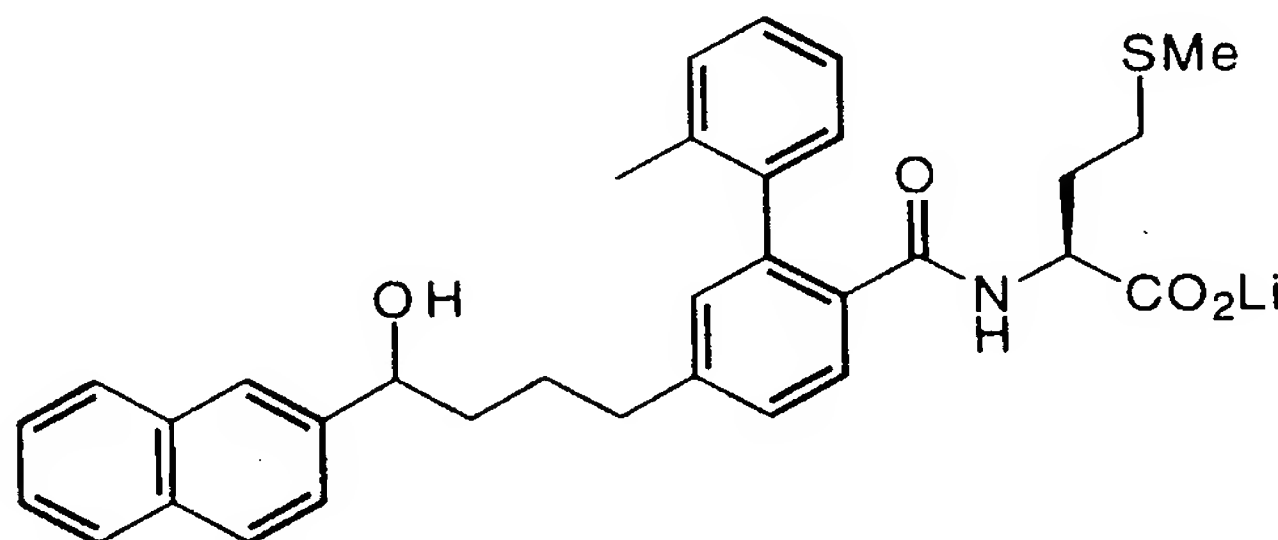
The desired compound was prepared according to the method of Examples 210 and 211.. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.46 (m, 2 H), 7.25-7.09 (m, 6 H), 6.96 (m, 1 H), 6.40 (m, 1 H), 3.64 (m, 1 H), 3.18 (m, 2 H), 2.2-2.05 (m, 2 H), 2.03-1.92 (3 br s's, 6 H), 1.75-0.90 (m, 13 H). MS (ESI -): m/e 464 (M-H)<sup>-</sup>.

6985

Example 472N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine

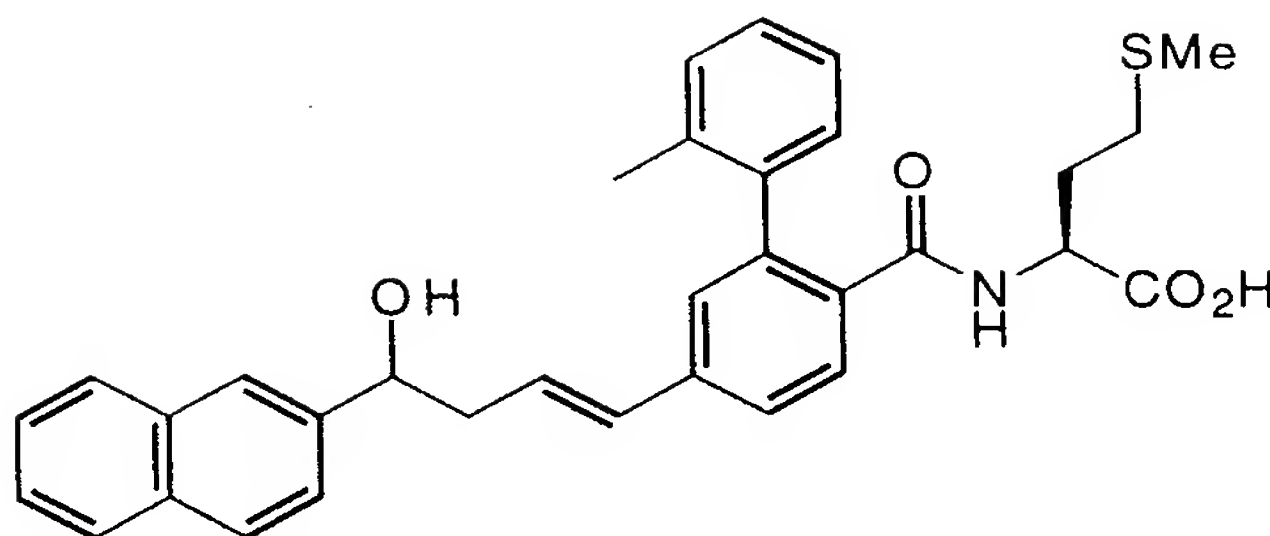
6990 The desired compound was prepared according to the method of Examples 210 and 211. <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub>): δ 7.98 (m, 1 H), 7.50-7.10 (m, 12 H), 6.41 (m, 1 H), 5.88 (m, 1 H), 4.57 (m, 1 H), 2.82 (m, 2 H), 2.57 (m, 2 H), 2.20-2.00 (m, 8 H), 1.92 (m, 1 H), 1.52 (m, 1 H). MS (CI +) m/e 474 (M+H)<sup>+</sup>.

6995

Example 473N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

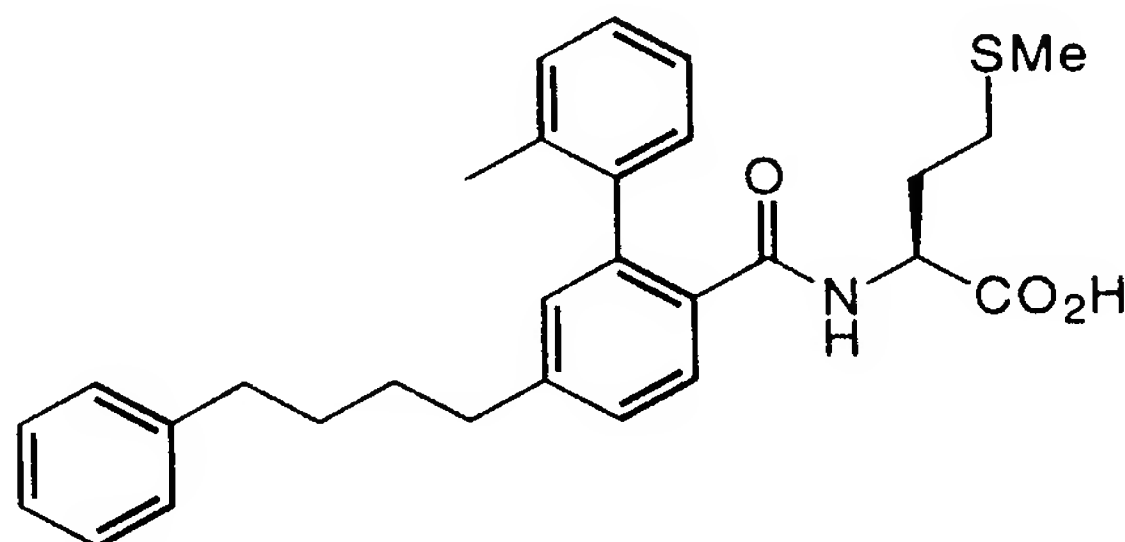
7000 The desired compound was prepared according to the method of Examples 210 - 212. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 8.61 (s, 1 H), 8.10 (br d, 1 H), 7.98 (m, 2 H), 7.63 (m, 2 H), 7.46 (m, 2 H), 7.31 (m, 1 H), 7.23-6.87 (m, 6 H), 3.44 (m, 1 H), 3.20 (m, 2 H), 2.75 (m, 2 H), 2.30-1.97 (m, 4 H), 1.95 (br s, 3 H), 1.91 (br s, 3 H), 1.90-1.56 (m, 2 H). MS (ESI -): m/e 538 (M-H)<sup>-</sup>.

7005

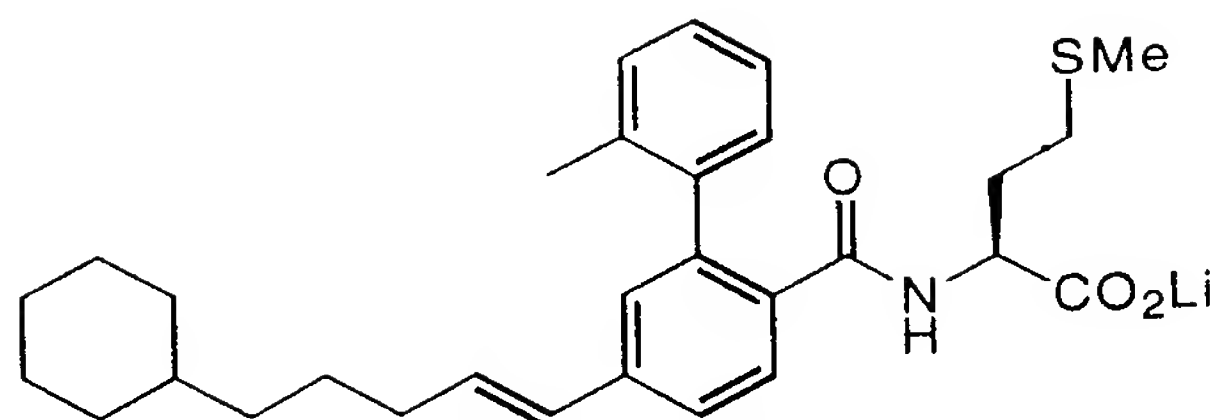
Example 474N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine

7010 The desired compound was prepared according to the method of Examples 210 and 211.  $^1\text{H}$  nmr (300 MHz, DMSO- $d_6$ ):  $\delta$  7.95-7.83 (m, 4 H), 7.56 (dd, 1 H), 7.48 (m, 3 H), 7.43 (m, 1 H), 7.25-7.08 (m, 5 H), 7.00-6.85 (m, 1 H), 6.45 (m, 1 H), 4.86 (t, 1 H), 3.64 (m, 1 H), 2.63 (br t, 2 H), 2.17 (m, 1 H), 1.98, 1.91 (2 br s's, 6 H), 1.95 (m, 1 H), 1.90-1.56 (m, 2 H). MS (ESI  $-$ ):  $m/e$  538 ( $M-H$ ) $^-$ .

7015

Example 478N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt

7020 The desired compound was prepared according to the method of Examples 210 - 212.  $^1\text{H}$  nmr (300 MHz, DMSO- $d_6$ ):  $\delta$  7.45 (d, 1 H), 7.27-7.10 (m, 5 H), 6.96 (m, 1 H), 6.89 (br s, 1 H), 3.67 (m, 1 H), 2.62 (t, 2 H), 2.15 (m, 1 H), 1.98, 1.91 (2 br s's, 6 H), 1.97 (m, 1 H), 1.70-0.75 (m, 19 H). MS (ESI  $-$ ):  $m/e$  480 ( $M-H$ ) $^-$ .

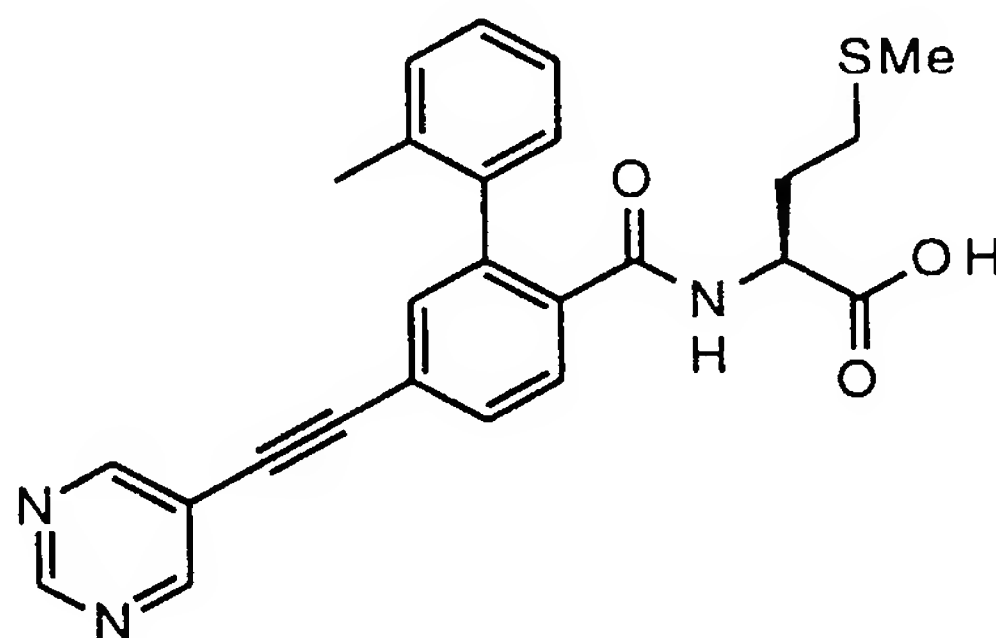


7025

Example 480N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 and 211.  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.00 (tt, 1 H), 7.43 (dt, 1 H), 6.38-7.15 (m, 11 H), 6.39 (m, 1 H), 5.85 (m, 1 H), 4.52 (m, 1 H), 2.70 (m, 2 H), 2.19 (m, 1 H), 2.20-2.00 (4 s's, 6 H), 2.10 (m, 3 H), 1.90-1.50 (m, 4 H). MS (CI +): m/e 488 ( $\text{M}+\text{H}$ ) $^+$ .

7030

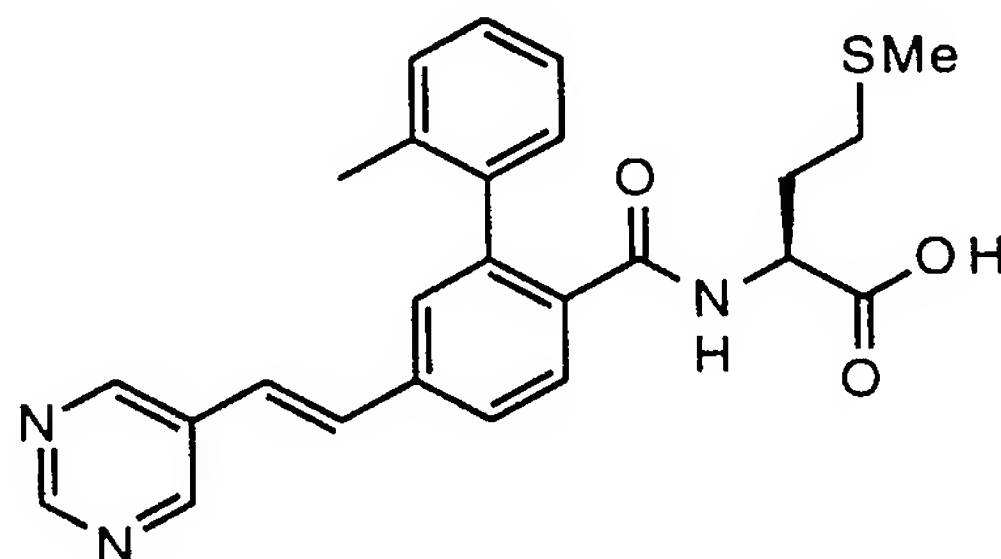


7035

Example 493N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

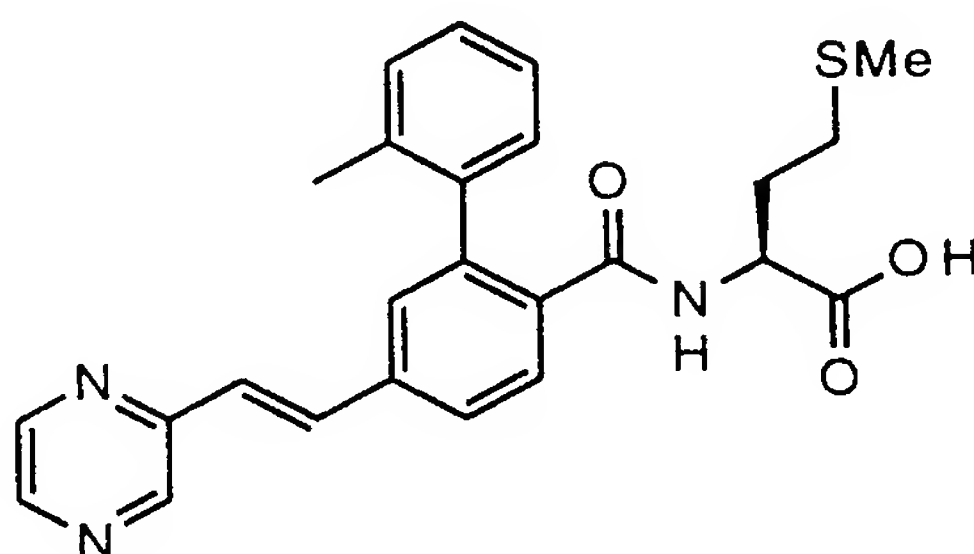
The desired compound was prepared according to the method of Examples 210 - 211.  $^1\text{H}$  nmr (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.20 (s, 1 H), 9.04 (s, 2 H), 7.63 (m, 3 H), 7.42 (m, 1 H), 7.30-7.18 (m, 4 H), 7.16-7.00 (m, 2 H), 3.48 (m, 1 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H).

7040

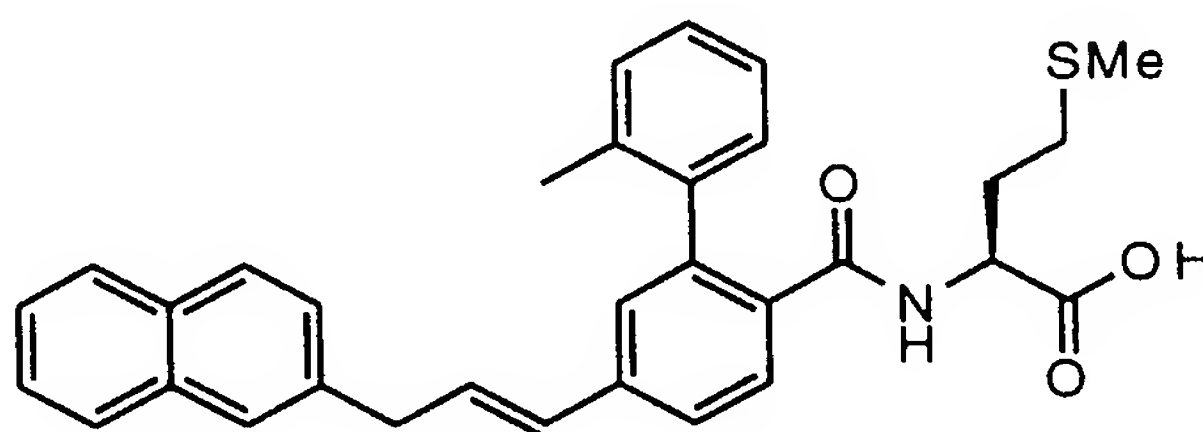
Example 494

7045 N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211  
<sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 9.06 (s, 1 H), 9.04 (s, 2 H), 7.67 (br d, 1 H), 7.00 (m, 2 H), 7.47 (m, 1 H), 7.38 (d, 1 H), 7.30-7.15 (m, 3 H), 7.10-6.97 (m, 2 H), 3.66 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -):  
 7050 m/e 446 (M-H)<sup>-</sup>.

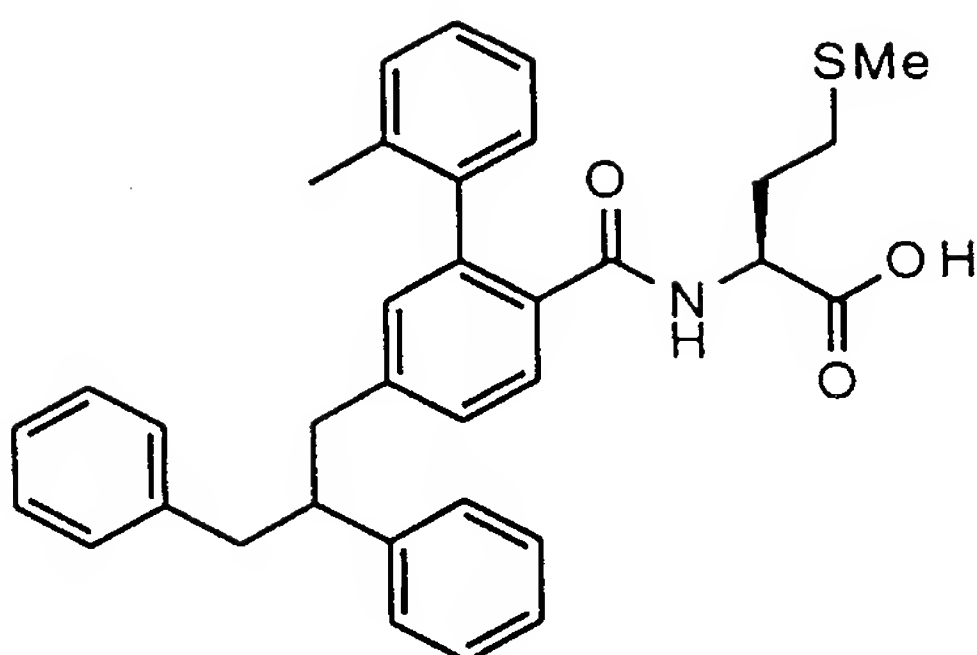
Example 4957055 N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211  
<sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 8.78 (s, 1 H), 8.63 (dd, 1 H), 8.51 (d, 1 H), 7.82 (d, 1 H), 7.76 (dd, 1 H), 7.59 (d, 1 H), 7.52 (m, 2 H), 7.30-7.10 (m, 4 H), 7.02 (m, 1 H), 3.68 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.93 (br s, 16 H), 1.70 (m, 1 H), 1.58 (m, 1 H).  
 7060 MS (ESI -): m/e 446 (M-H)<sup>-</sup>.

Example 4967065 N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt  
(1:1 mixture of olefin isomers)

The desired compound was prepared according to the method of Examples 210 - 211  
<sup>1</sup>H nmr (300 MHz, MeOD-d<sub>4</sub>): δ 7.85-7.58 (m, 5 H), 7.51-7.36 (m, 4 H), 7.32-7.10 (m, 5 H), 6.61 (m, 1 H), 4.24 (m, 1 H), 3.72, 3.67 (2 d's, 2 H, 1:1 ratio), 2.24 (m, 1 H), 2.08-  
 7070 1.95 (4 s's, 6 H), 1.99 (m, 1 H), 1.90-1.60 (m, 2 H). MS (ESI -) m/e 508 (M-H)<sup>-</sup>.

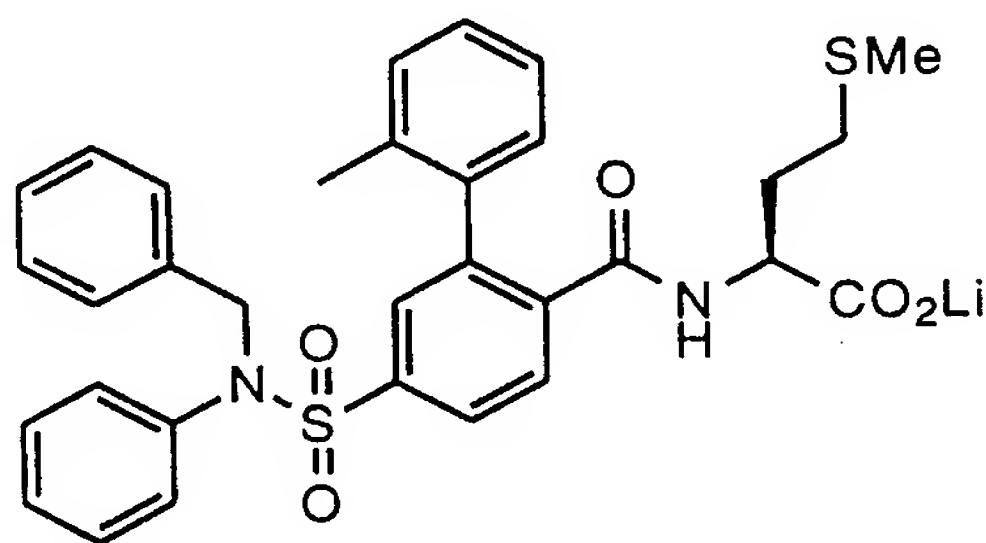


Example 572

7075 N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212 (DMSO-d<sub>6</sub>)  $\delta$  7.38 (d, 1H), 7.10, 6.90, 6.73 (all m, total 17H), 3.75 (m, 1H), 2.98 (m, 5H), 2.10-1.50 (envelope, 10H). MS (ESI) 536 (M-H)<sup>-</sup>. Anal calcd for C<sub>34</sub>H<sub>34</sub>LiNO<sub>3</sub>S · 0.25 H<sub>2</sub>O: C, 74.50; H, 6.34; N, 2.56. Found: C, 7.10; H, 5.95; N, 2.53.

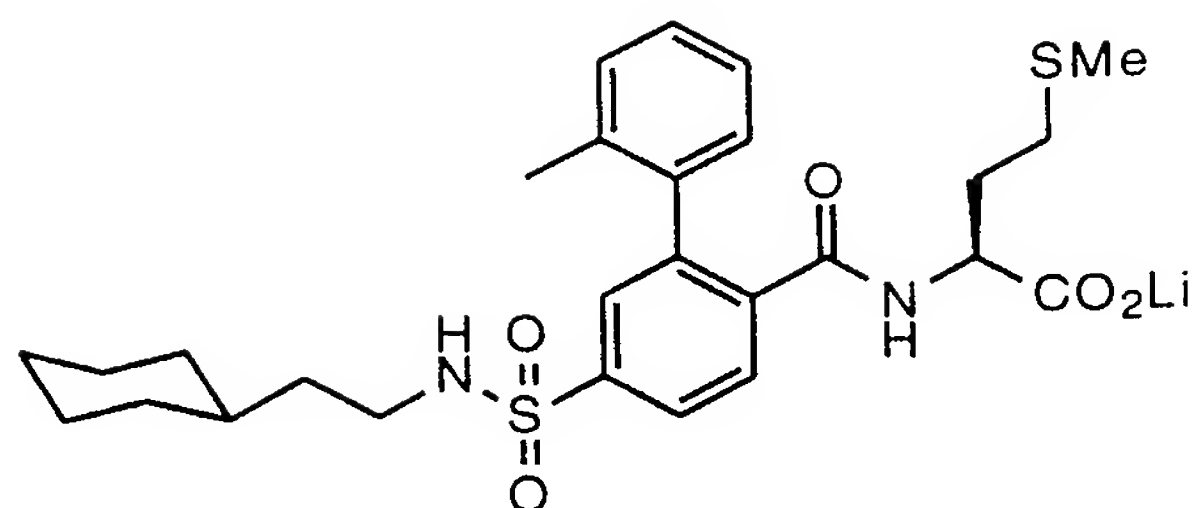
7080

Example 768

7085 N-[4-(N-Benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

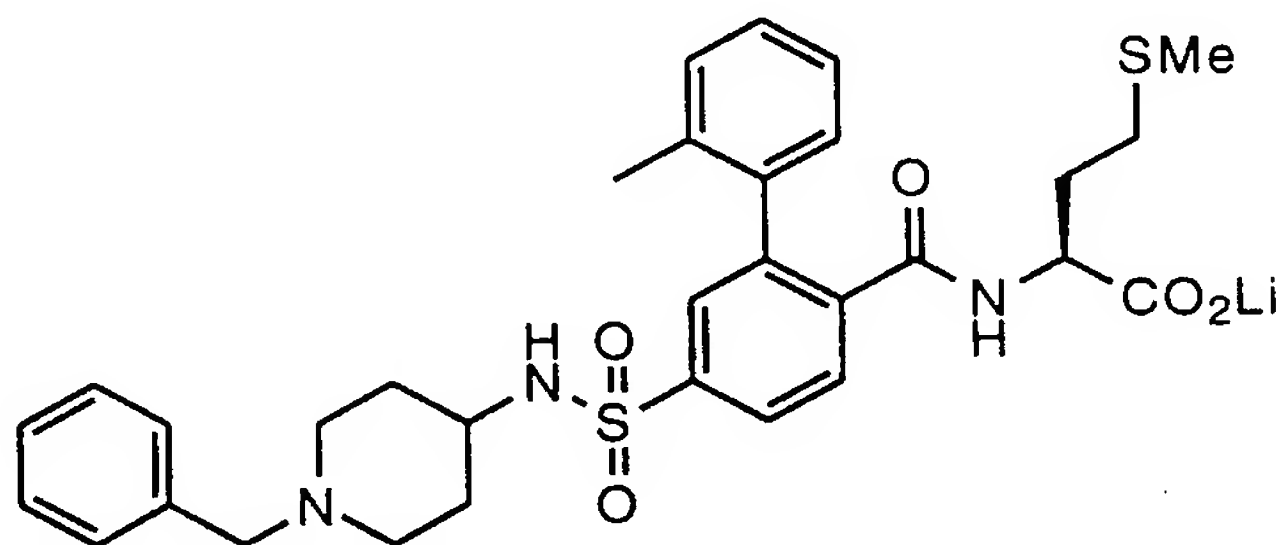
The desired compound was prepared according to the method of Example 5E. <sup>1</sup>H (d<sub>6</sub>-DMSO):  $\delta$  7.7-7.9 (4H, m); 7.3-7.1 (13H, m); 4.84 (2H, s); 4.1 (1H, m) 3.2 (3H, s); 1.9 (3H, s); 2.1-1.6 (4H, m). ESI(-)/MS: 587 (M-Li)

7090

Example 772

N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

7095 The desired compound was prepared according to the method of Example 5E.  $^1\text{H}$  (CD<sub>3</sub>OD): 7.85-7.9 (1H, d); 7.7-7.8 (1H, d); 7.6-7.7 (1H, s); 7.2-7.3 (4H, m); 4.2-4.3 (1H, m); 2.8-2.9 (2H, t); 2.05-2.1 (2H, m); 2.0 (3H, s); 1.9 (3H, s); 1.6-1.7 (6H, m) 1.1-1.4 (7H, m); 1.7-1.86 (2H, m). ESI(-)/MS: 521(M-Li); 487, 459.

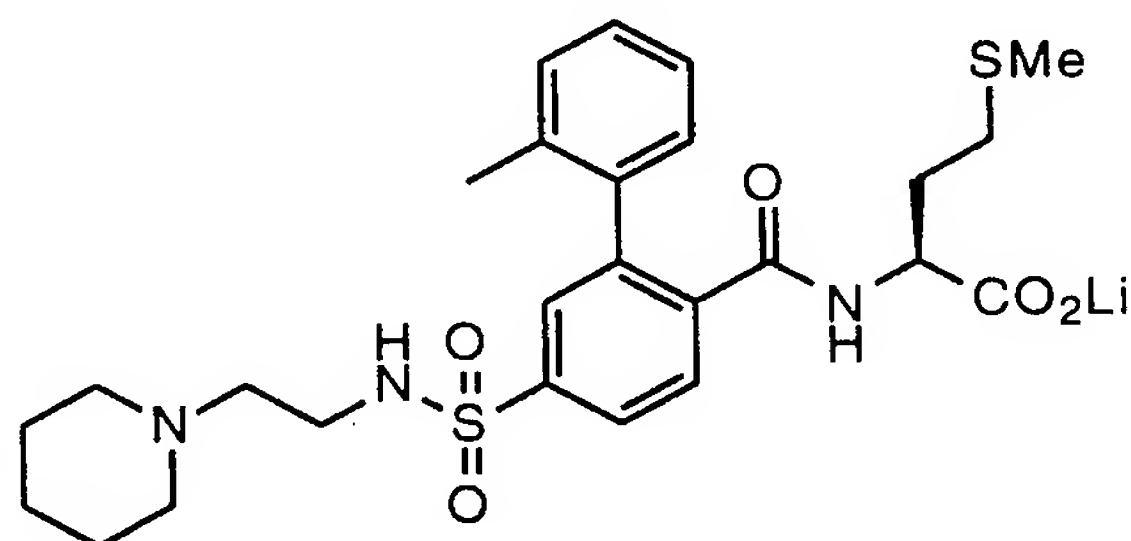


7100

Example 773

N-[4-(1-Benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

7105 The desired compound was prepared according to the method of Example 5E.  $^1\text{H}$  (CD<sub>3</sub>OD): 7.82-7.94 (1H, d); 7.75-7.81 (1H, d); 7.62-7.72 (1H, s); 7.1-7.38 (9H, m); 4.2-4.3 (1H, m); 3.1(2H, s); 3.0-3.1 (1H, m); 2.7-2.8 (2H, d); 2.42-2.54 (2H, t); 1.78-2.3 (11H, m); 1.6-1.78 (3H, m); 1.4-1.6 (2H, m). ESI(-)/MS: 594(M-Li).

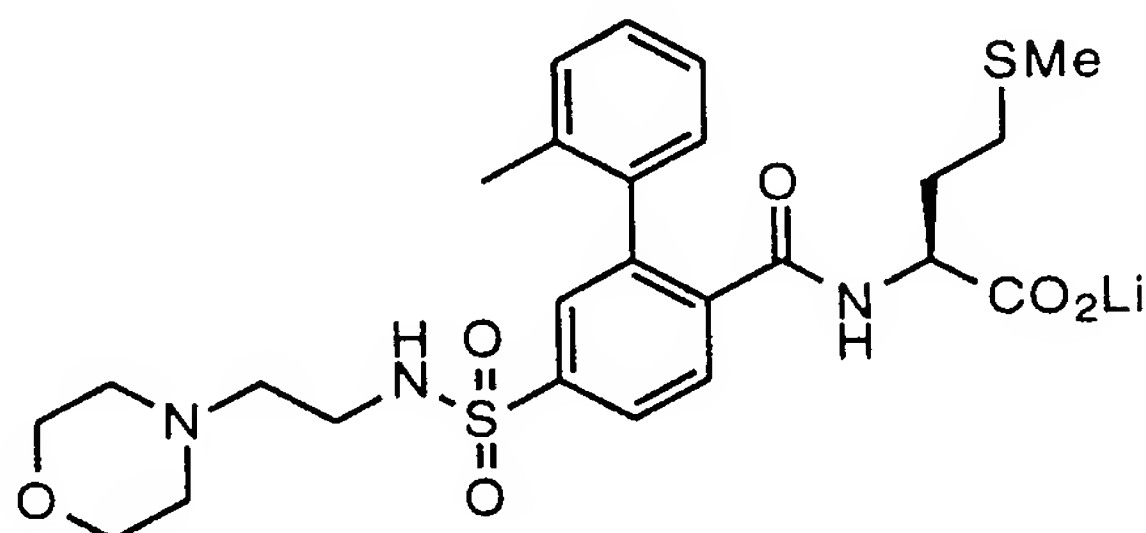


7110

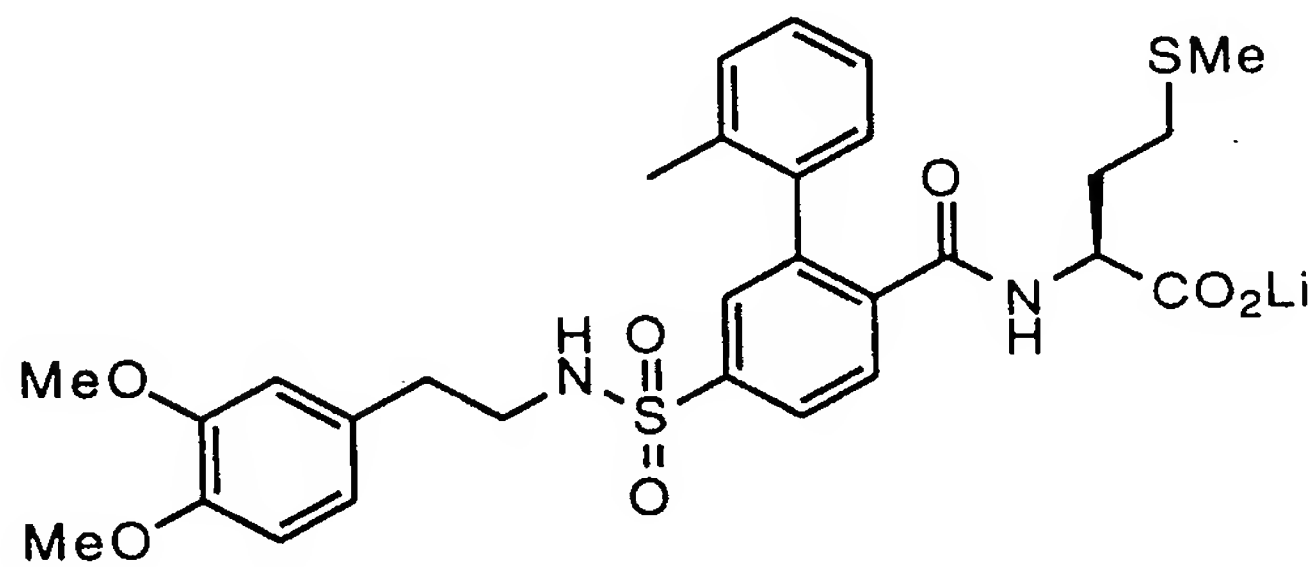
Example 774

*N*-[4-*N*-(2-piperidin-1ylethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

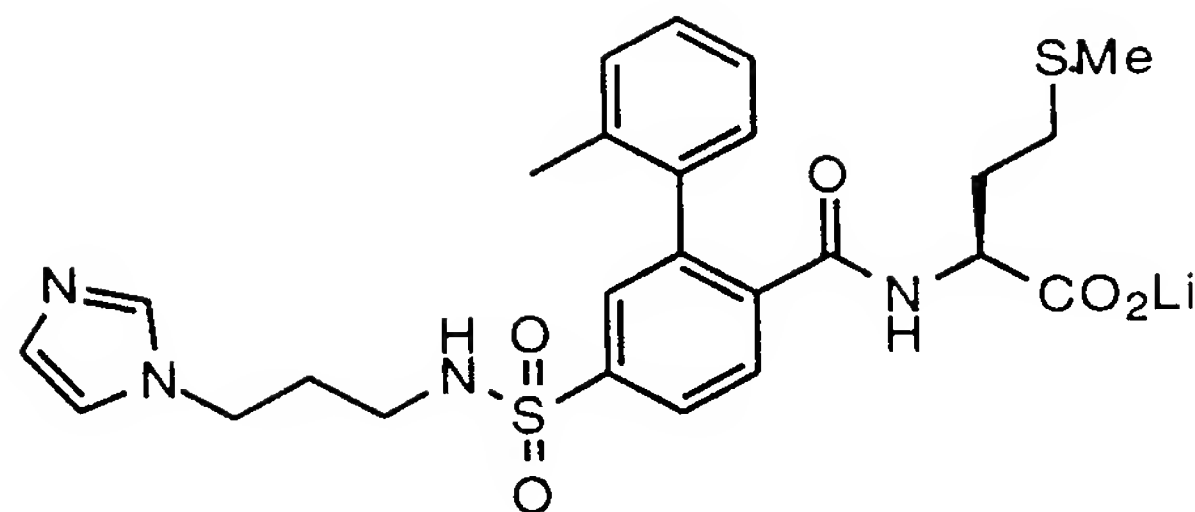
The desired compound was prepared according to the method of Example 5E. <sup>1</sup>H (CD<sub>3</sub>OD): 7.82-7.94 (1H, d); 7.75-7.81 (1H, d); 7.62-7.72 (1H, s); 7.1-7.38 (4H, m); 4.18-4.3 (1H, m); 3.1(2H, m); 2.34-2.5 (5H, m); 2.2-2.35 (2H, m); 2.05-2.2 (2H, m); 1.93-2.05 (3H, s); 1.8-1.95 (4H, m); 1.6-1.7 (2H, m); 1.55-1.6 (3H, m); 1.4-1.5 (2H, m). ESI(-)/MS: 532 (M-Li); 488; 357.

Example 775*N*-[4-*N*-(2-morpholin-1ylethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 5E. <sup>1</sup>H (CD<sub>3</sub>OD): 7.9-8.1 (1H, d); 7.8-7.9 (1H, d); 7.67-7.8 (1H, s); 7.1-7.4 (4H, m); 4.2-4.3 (1H, m); 3.4-3.7 (4H, m); 3.4-3.2 (4H, m); 2.9-3.2 (2H, t); 1.6-2.6 (12H, m) ESI(-)/MS: 534(M-Li); 490; 462.

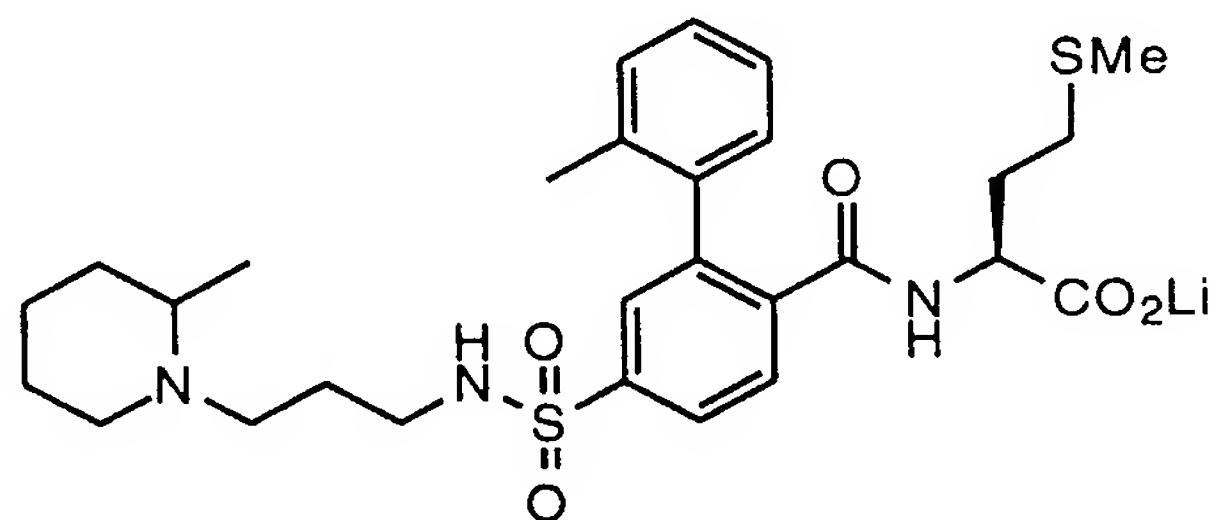
Example 776*N*-[4-(2-(3,4-dimethoxyphenyl)ethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 5E. <sup>1</sup>H(MeOH-*d*<sub>4</sub>): δ 7.78-7.9 (2H, m); 7.62-7.7 (1H, s); 7.1-7.3 (4H, m); 6.78-6.82 (1H, d); 6.72-6.78 (1H, d); 6.65-6.72 (1H, q); 4.2-4.3 (1H, m); 3.75-3.8 (6H, s); 3.08-3.18 (2H, m); 2.58-2.7 (2H, t); 1.6- 2.26 (10H, m). ESI(-)/MS: 585(M-Li); 541; 410.

Example 777N-[4-(3-imidazol-1-ylpropylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

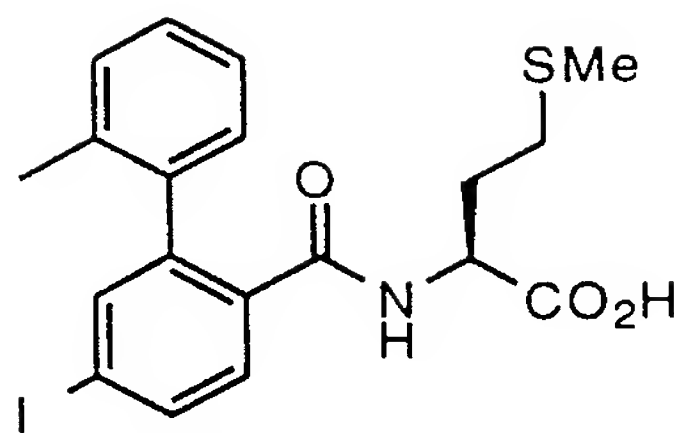
7140 The desired compound was prepared according to the method of Example 5E.  
<sup>1</sup>H(MeOH-d<sub>4</sub>): δ 7.78-7.9 (2H, dd); 7.5-7.6 (2H, m); 7.1-7.3 (4H, m); 7.1 (1H, s); 6.92 (1H, s); 4.2-4.3 (1H, m); 4.05-4.18 (2H, t); 2.8-2.9 (2H, t); 1.6-2.3 (12H, m). ESI(-)/MS: 529(M-Li); 281; 255.

7145

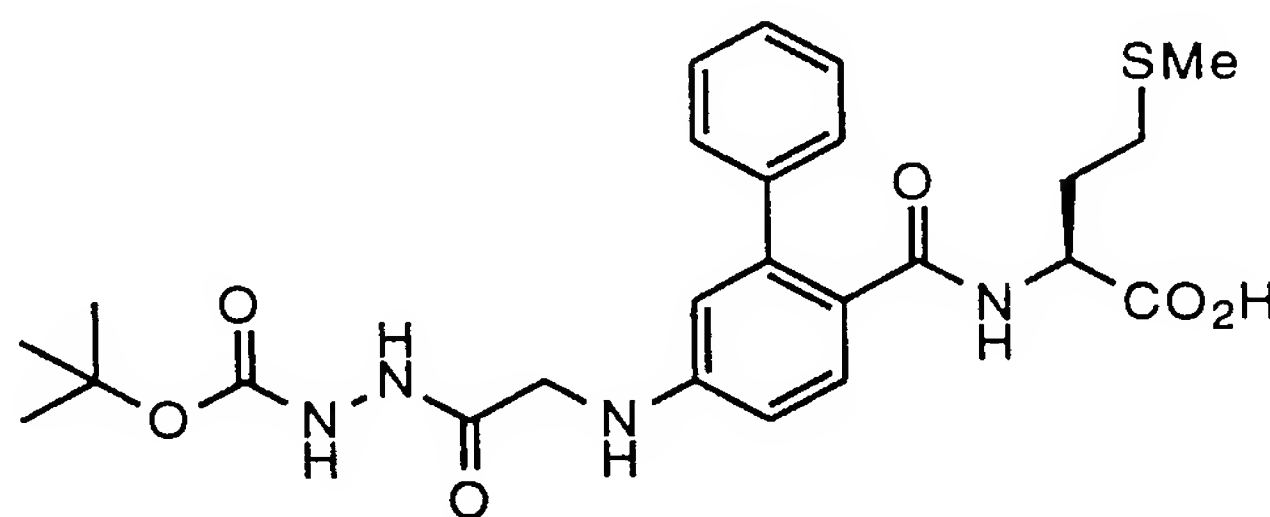
Example 778N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

7150 The desired compound was prepared according to the method of Example 5E.  
<sup>1</sup>H(MeOH-d<sub>4</sub>): δ 7.8-7.94(2H, dd); 7.6-7.7 (1H, s); 7.1-7.4 (4H, m); 4.2-4.3 (1H, m); 2.84-2.94 (2H, t); 2.7-2.87 (2H, m); 1.8- 2.5 (13H, m); 1.4-1.8 (6H, m); 1.24-1.349 (2H, m); 1.0-1.1 (3H, m). ESI(-)/MS: 560(M-Li); 385; 281.

7155

Example 783N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine

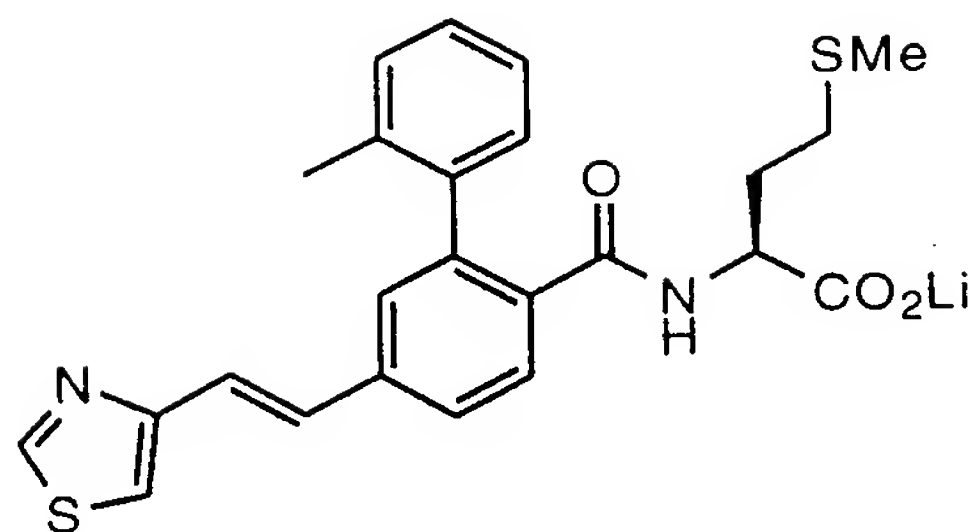
7160 The desired compound was prepared according to the method of Example 210C. <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub>): δ 7.83 (dd, 1 H), 7.72 (dd, 1 H), 7.60 (s, 1 H), 7.39-7.16 (m, 4 H), 5.89 (m, 1 H), 4.58 (m, 1 H), 2.20-2.00 (m, 8 H), 1.96 (m, 1 H), 1.58 (m, 1 H). MS (CI +) m/e 452 (M+H)<sup>+</sup>.



7165

Example 784N-[4-N(t-Butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine

7170 The desired compound was prepared according to the method of Example 57, except t-Butylcarbazatocarbonylmethyl bromide was used as the alkylating agent. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 9.79 (s, 1 H), 8.85 (s, 1 H), 8.12 (d, 1 H), 7.47-7.29 (m, 6 H), 6.65 (br d, 1 H), 6.56 (d, 1 H), 6.43 (t, 1 H), 4.30 (m, 1 H), 3.81 (d, 2 H), 2.32 (m, 2 H), 2.05 (br s, 6 H), 1.90 (m, 2 H), 1.47 (s, 9 H). MS (APCI +) m/e 517 (M+H)<sup>+</sup>.

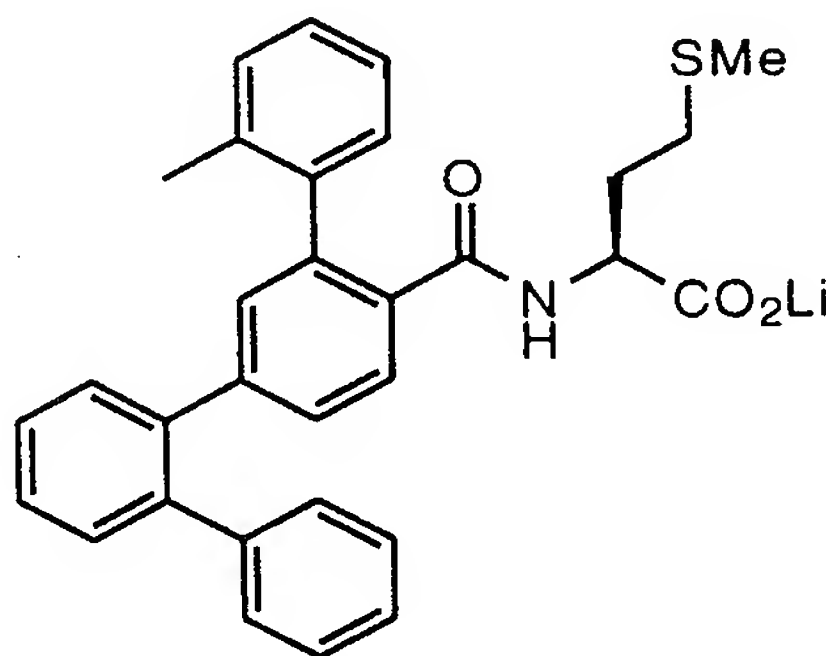


7175

Example 785N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 9.01 (s, 1 H), 7.98 (s, 1 H), 7.67 (d, 1 H), 7.63 (m, 1 H), 7.55 (d, 1 H), 7.42 (m, 1 H), 7.30-7.15 (m, 4 H), 3.65 (m, 1 H), 2.18 (m, 2 H), 2.02 (br s, 3 H), 1.92 (br s, 3 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 451 (M-H)<sup>-</sup>.

7180

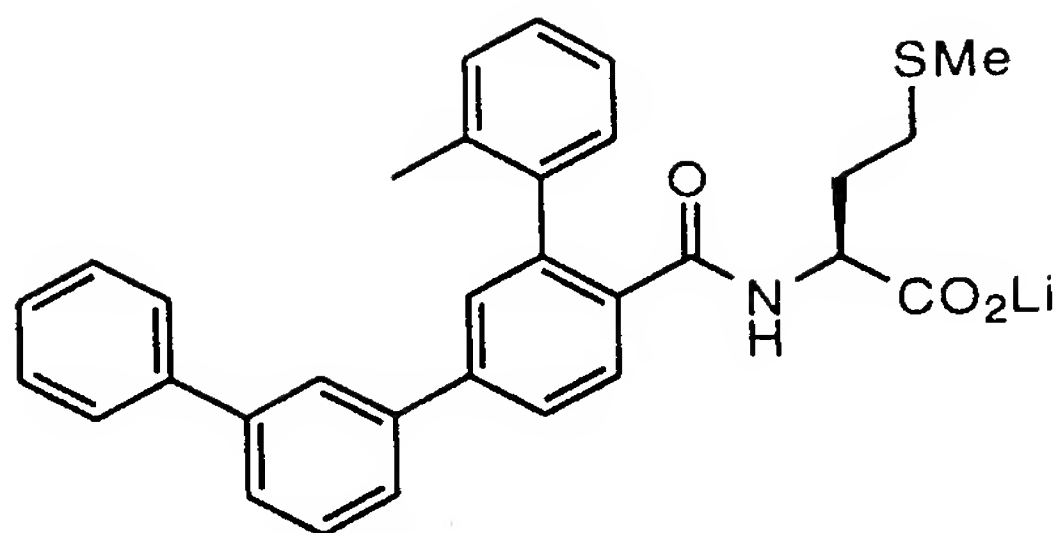


7185

Example 786N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.96 (s, 1 H), 7.83 (d, 1 H), 7.77 (d, 2 H), 7.74 (d, 1 H), 7.66 (t, 2 H), 7.56 (t, 2 H), 7.48 (t, 2 H), 7.38 (t, 1 H), 7.24 (m, 3 H), 7.02 (m, 1 H), 3.66 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)<sup>-</sup>.

7190

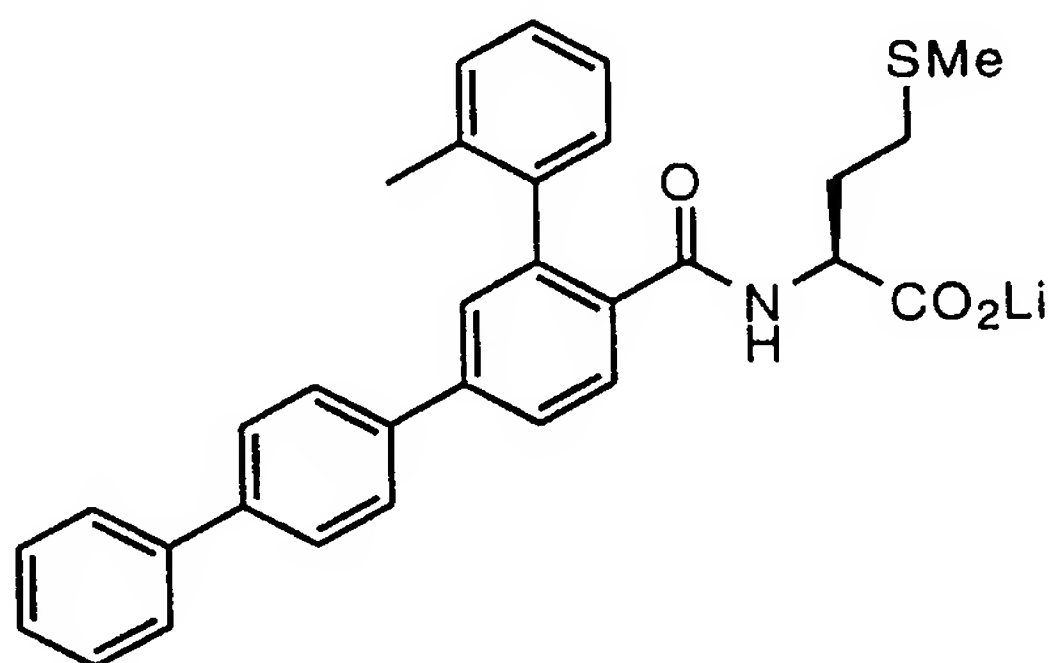


7195

Example 787N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.754-7.44 (m, 4 H), 7.51 (m, 1 H), 7.38 (m, 1 H), 7.34-7.22 (m, 3 H), 7.19-7.00 (m, 5 H), 6.90-6.85 (m, 2 H), 6.66 (m, 1 H), 3.62 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)<sup>-</sup>.

7200

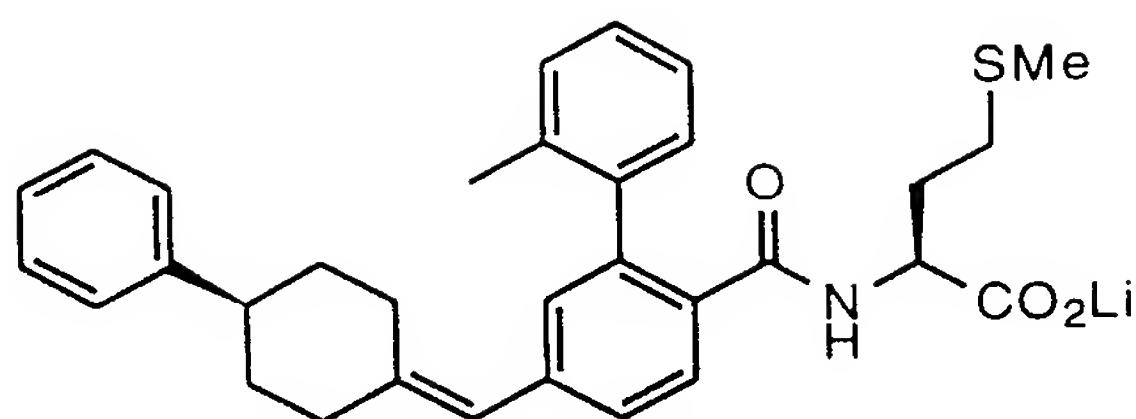


7205

Example 788N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.87-7.80 (m, 3 H), 7.78 (t, 2 H), 7.73 (d, 2 H), 7.65 (d, 1 H), 7.49 (m, 3 H), 7.39 (m, 1 H), 7.33-7.15 (m, 4 H), 7.02 (m, 1 H), 3.66 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)<sup>-</sup>.

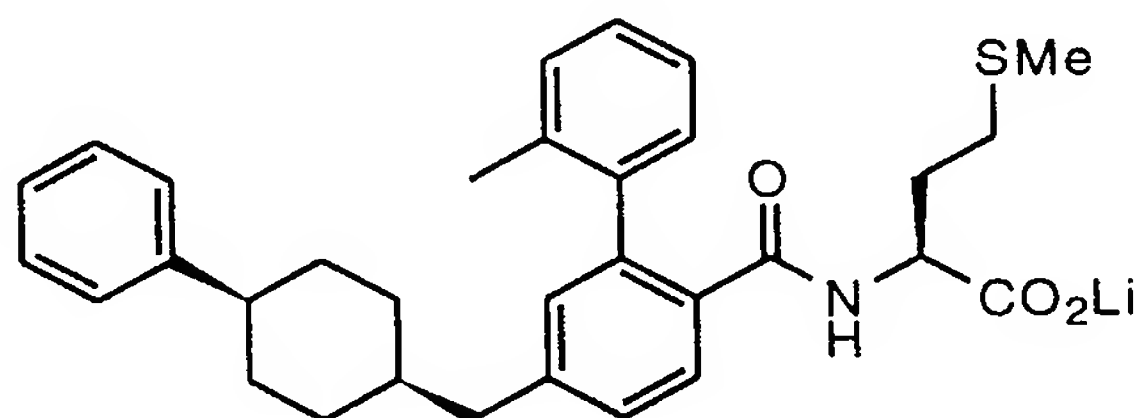
7210



Example 789

N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. <sup>1</sup>H nmr (300 MHz, CD<sub>3</sub>OD): δ 7.56 (m, 1 H), 7.25-6.94 (m, 10 H), 6.27 (s, 1 H), 4.16 (m, 1 H), 2.60 (m, 1 H), 2.40 (m, 2 H), 2.17 (m, 2 H), 2.00-1.70 (m, 13 H), 1.58 (m, 1 H). MS (ESI -): m/e 522 (M-H)<sup>-</sup>.

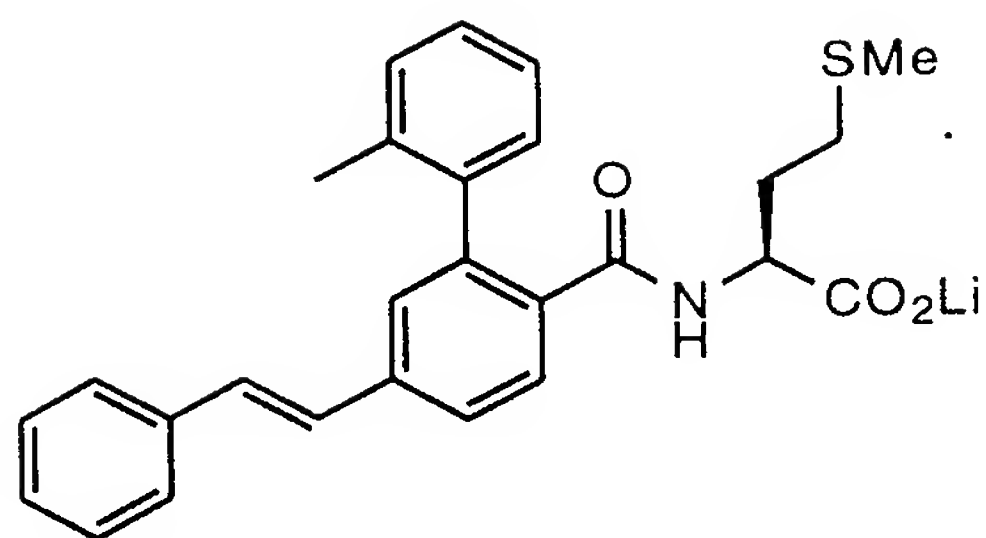


Example 790

N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. <sup>1</sup>H nmr (300 MHz, CD<sub>3</sub>OD): δ 7.53 (m, 2 H), 7.22-6.92 (m, 10 H), 4.15 (m, 1 H), 2.73 (br d, 2 H), 2.52 (m, 1 H), 2.15 (m, 2 H), 2.02-1.90 (m, 6 H), 1.75 (m, 5 H), 1.57 (m, 5 H). MS (ESI -): m/e 514 (M-H)<sup>-</sup>.



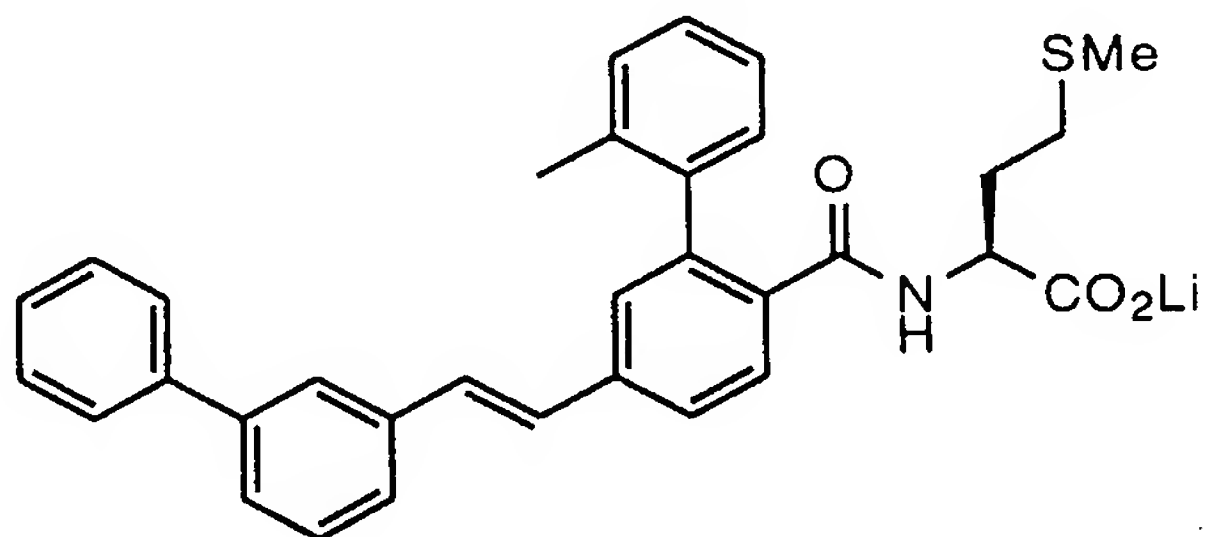
Example 791

7235

N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

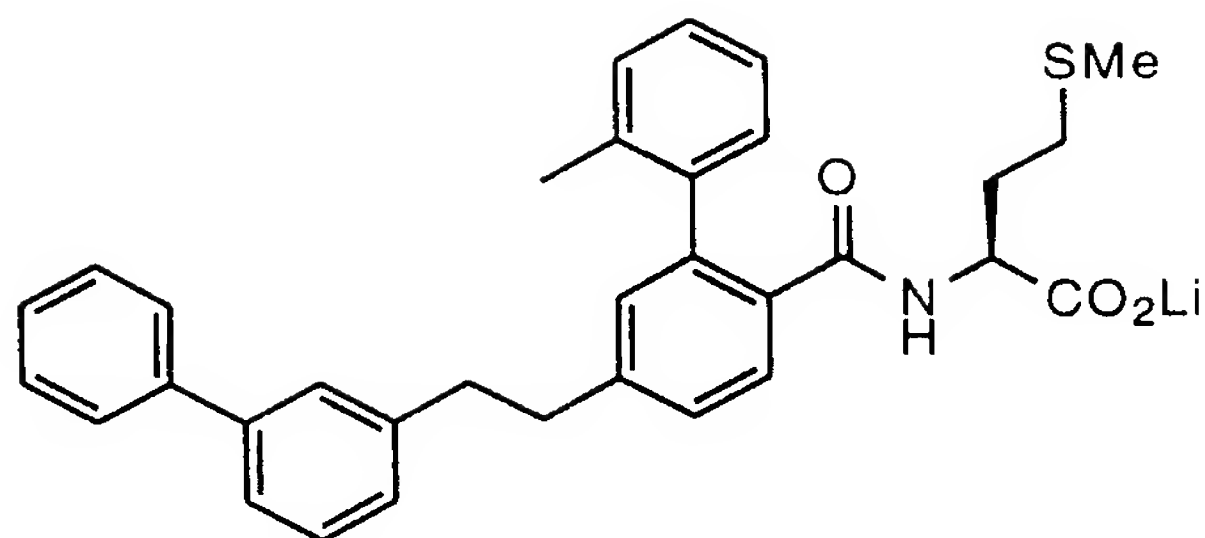
The desired compound was prepared according to the method of Examples 210 - 211.  $^1\text{H}$  nmr (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.03 (dd, 1 H), 7.61 (dd, 1 H), 7.52 (m, 2 H), 7.40-7.22 (m, 8 H), 7.20 (d, 1 H), 7.10 (d, 1 H), 5.93 (m, 1 H), 4.59 (m, 1 H), 2.20-2.00 (m, 8 H), 1.96 (m, 1 H), 1.56 (m, 1 H). MS (CI +) m/e 446 ( $\text{M}+\text{H}$ ) $^+$ .

7240

Example 792N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

7245

The desired compound was prepared according to the method of Examples 210 - 211.  $^1\text{H}$  nmr (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.83-7.10 (m, 18 H), 4.27 (m, 1 H), 2.30 (m, 1 H), 2.15-1.95 (m, 8 H), 1.88 (m, 1 H), 1.69 (m, 1 H). MS (ESI -): m/e 520 ( $\text{M}-\text{H}$ ) $^-$ .



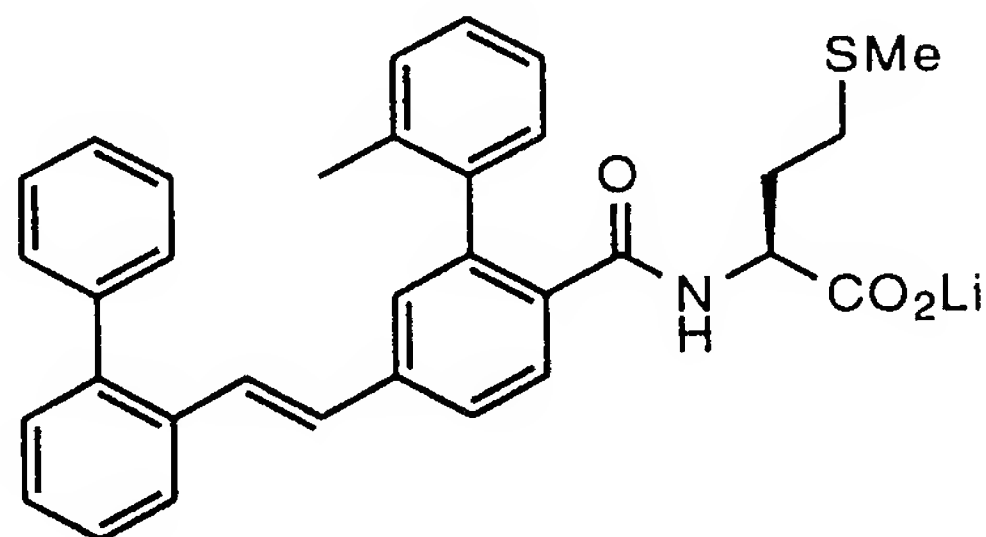
7250

Example 793N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.

<sup>1</sup>H nmr (300 MHz, CD<sub>3</sub>OD): δ 7.60 (br d, 1 H), 7.51 (br d, 2 H), 7.45-7.20 (m, 12 H), 6.98 (m, 1 H), 4.23 (m, 1 H), 3.04 (br s, 4 H), 2.12 (m, 2 H), 2.03-1.91 (m, 6 H), 1.83 (m, 1 H), 1.65 (m, 1 H). MS (ESI -): m/e 522 (M-H)<sup>-</sup>.

7255



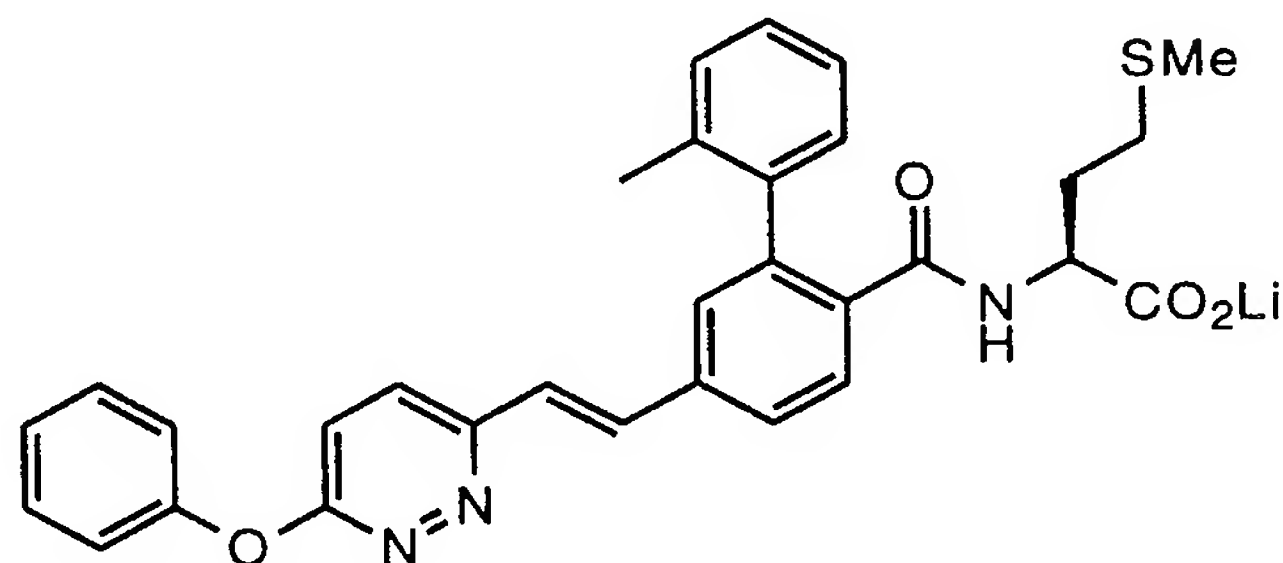
7260

Example 794N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.85 (dd, 1 H), 7.54-7.30 (m, 9 H), 7.30-7.10 (m, 6 H), 7.10 (d, 1 H), 6.95 (m, 1 H), 3.67 (m, 1 H), 2.16 (m, 2 H), 2.02 (br s, 3 H), 1.91 (br s, 3 H), 1.70 (m, 1 H), 1.57 (m, 1 H). MS (ESI -): m/e 521 (M-H)<sup>-</sup>.

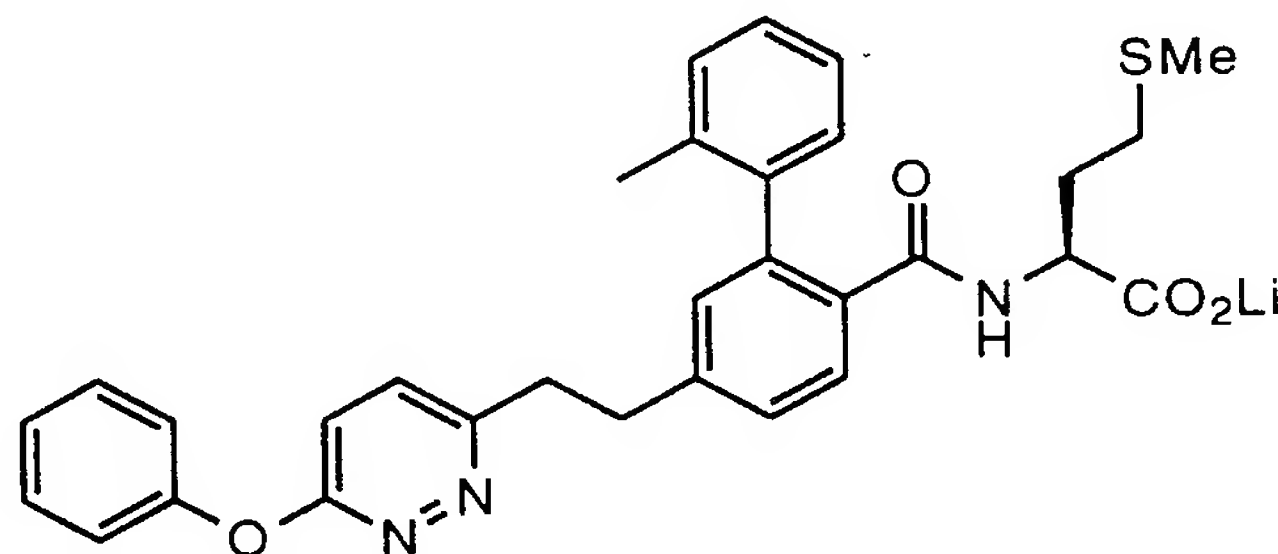
7265



Example 810

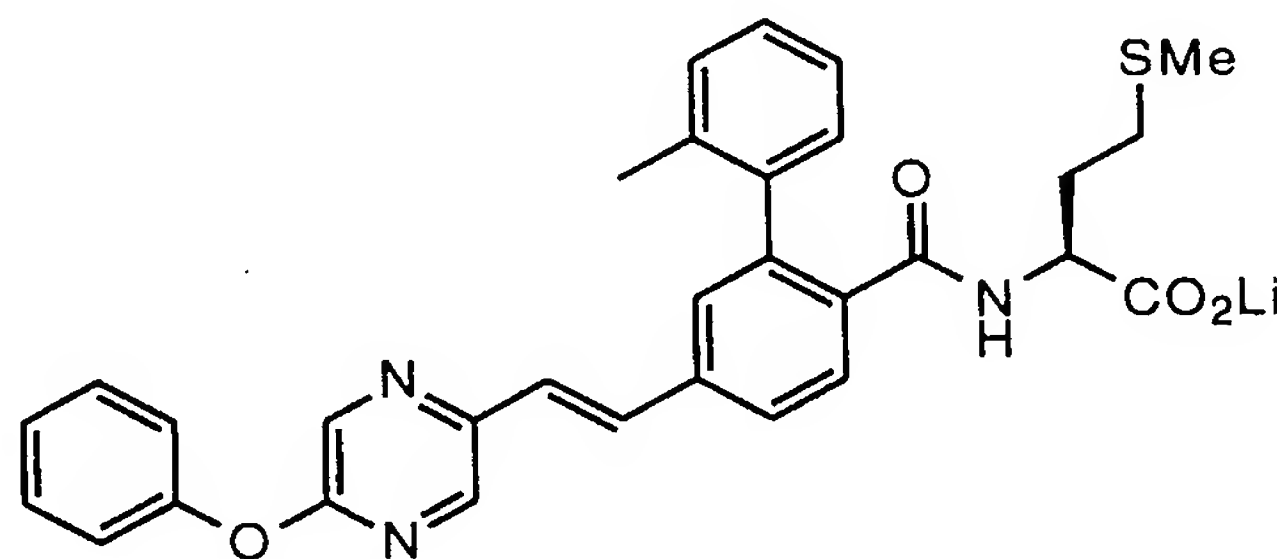
7270 *N*-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine  
lithium salt

The desired compound was prepared according to the method of Examples 210 -  
 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 8.08 (d, 1 H), 7.76 (dd, 1 H), 7.59 (d, 1 H), 7.52  
 (d, 1 H), 7.52-7.43 (m, 4 H), 7.31-7.10 (m, 7 H), 7.00 (m, 1 H), 2.18 (m, 1 H), 2.02 (m,  
 7275 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 538 (M-H)<sup>-</sup>.

Example 811

7280 *N*-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

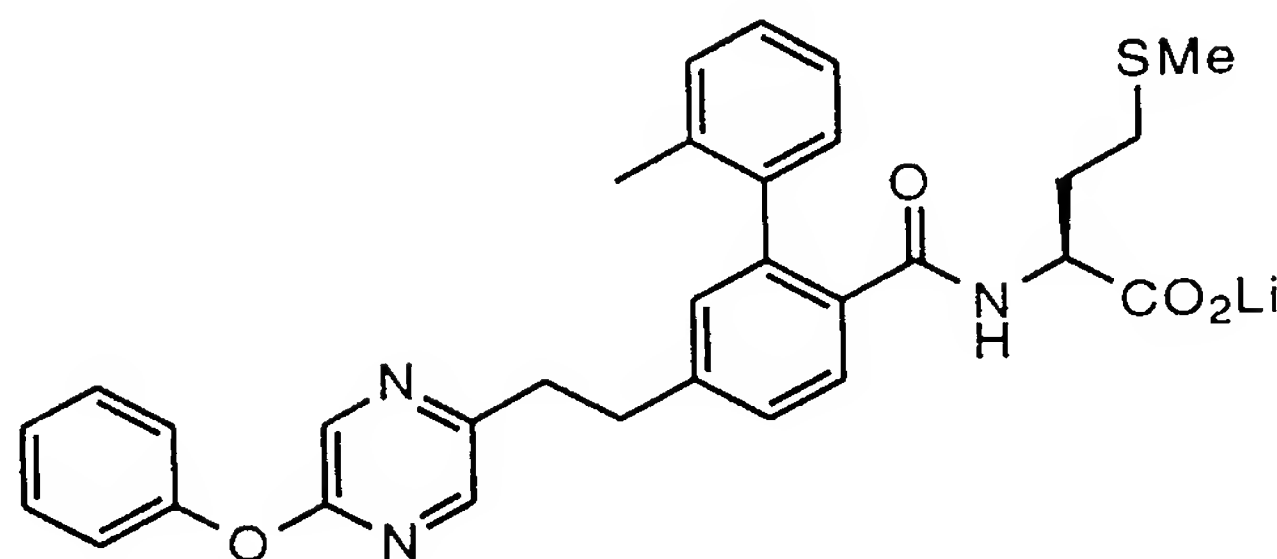
The desired compound was prepared according to the method of Examples 210 -  
 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 7.65 (d, 1 H), 7.46 (d, 1 H), 7.44 (d, 1 H), 7.38-  
 7.10 (m, 9 H), 6.94 (m, 1 H), 6.88 (m, 1 H), 6.75 (m, 1 H), 3.65 (m, 1 H), 3.19 (t, 2 H),  
 3.07 (t, 2 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1  
 7285 H). MS (ESI -): m/e 540 (M-H)<sup>-</sup>.

Example 812

7290 *N*-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine  
lithium salt

The desired compound was prepared according to the method of Examples 210 -  
 211. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 8.51 (s, 1 H), 8.33 (s, 1 H), 7.64 (m, 1 H), 7.53-

7.38 (m, 6 H), 7.30-7.15 (m, 7 H), 7.00 (m, 1 H), 3.65 (m, 1 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 538 (M-H)<sup>-</sup>.

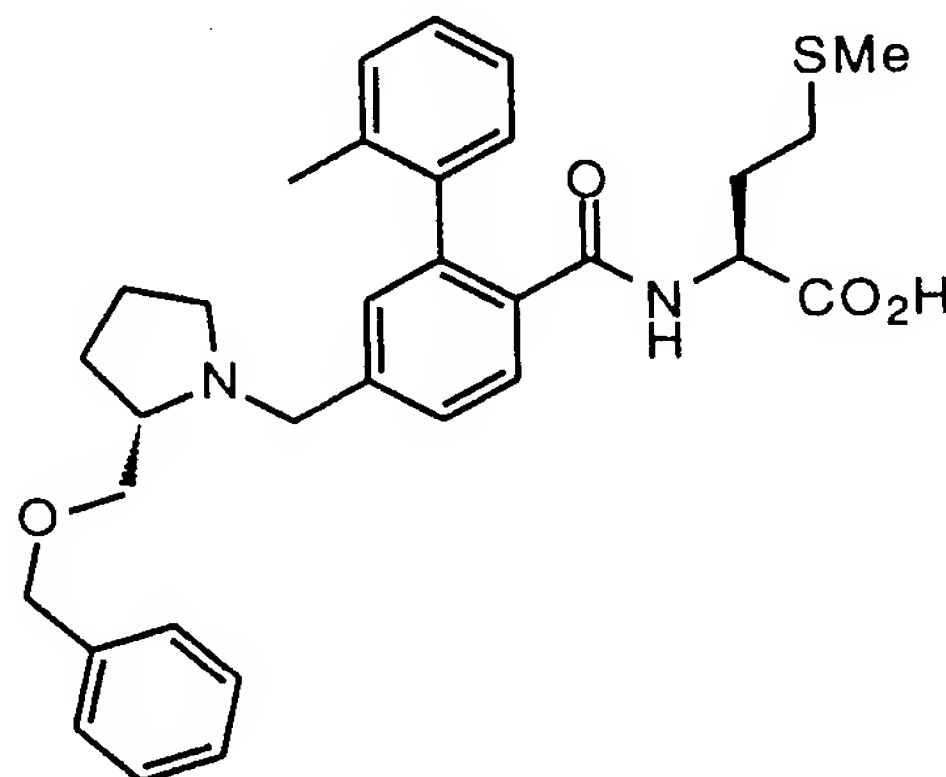


### Example 813

7300 N-[4-(2-(2-phenoxy)pyridazin-5-yl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. <sup>1</sup>H nmr (300 MHz, DMSO-d<sub>6</sub>): δ 8.26 (s, 1 H), 8.21 (s, 1 H), 7.50-7.30 (m, 6 H), 7.30-7.10 (m, 5 H), 7.00 (m, 1 H), 3.65 (m, 1 H), 2.97 (m, 4 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 540 (M-H)<sup>-</sup>.

7305

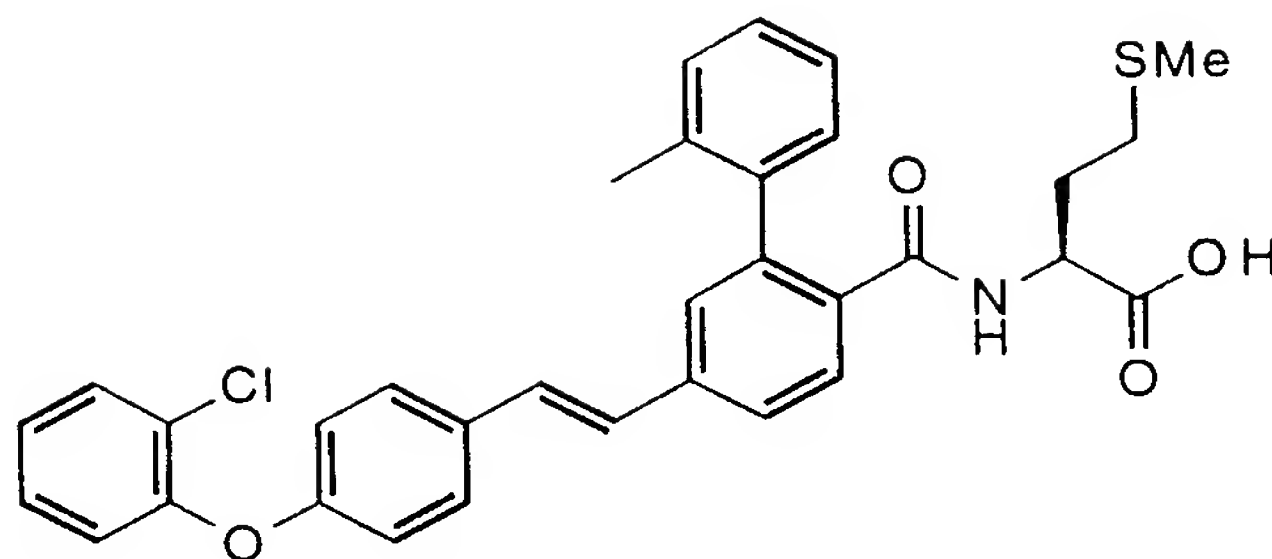


### Example 824

7310 N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157. <sup>1</sup>H nmr (300 MHz, DMSO d<sub>6</sub>): δ 8.13, d, 1H; 7.47, d, 1H; 7.37, d, 1H; 7.13 - 7.32, m, 10H; 4.48, s, 2H; 4.21, m 2H; 3.51, m, 2H; 3.38, m, 2H; 2.89, m, 2H; 1.99 - 2.40 m, 7H; 1.98, s, 3H; 1.50 - 1.96, m, 4H. MS (ESI(-)): 545 (M-H); (ESI(+)): 547. Calc'd for C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>S + 0.70 H<sub>2</sub>O: C 68.72, H 7.10, N 5.01: Found: C 68.71, H 6.688, N 4.92.

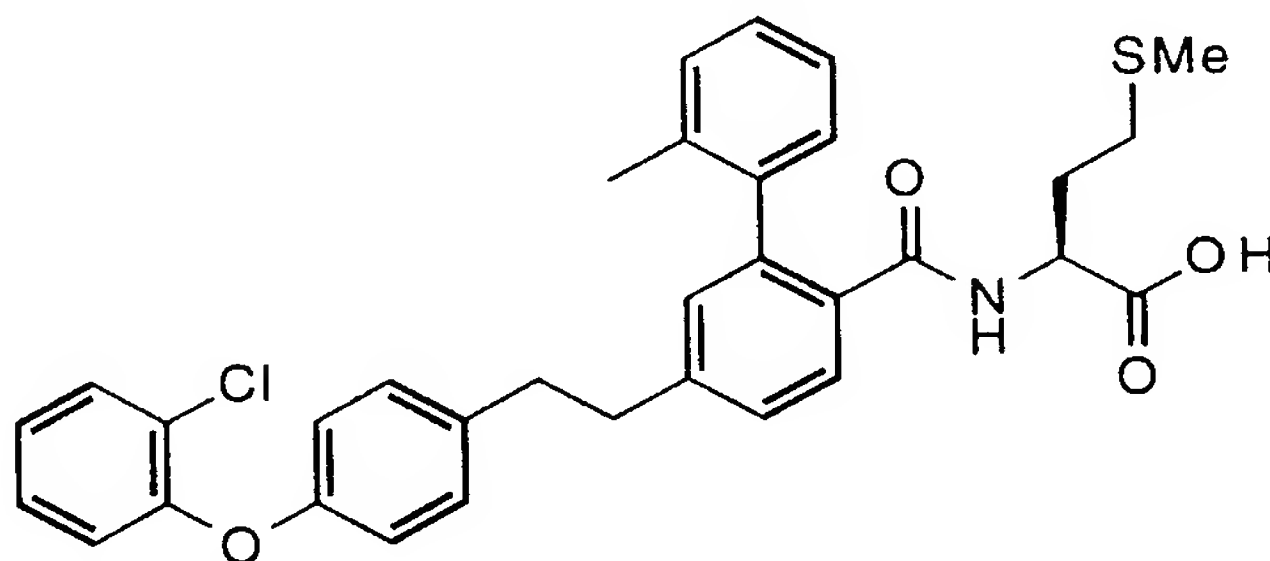
7315

Example 854

7320 N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

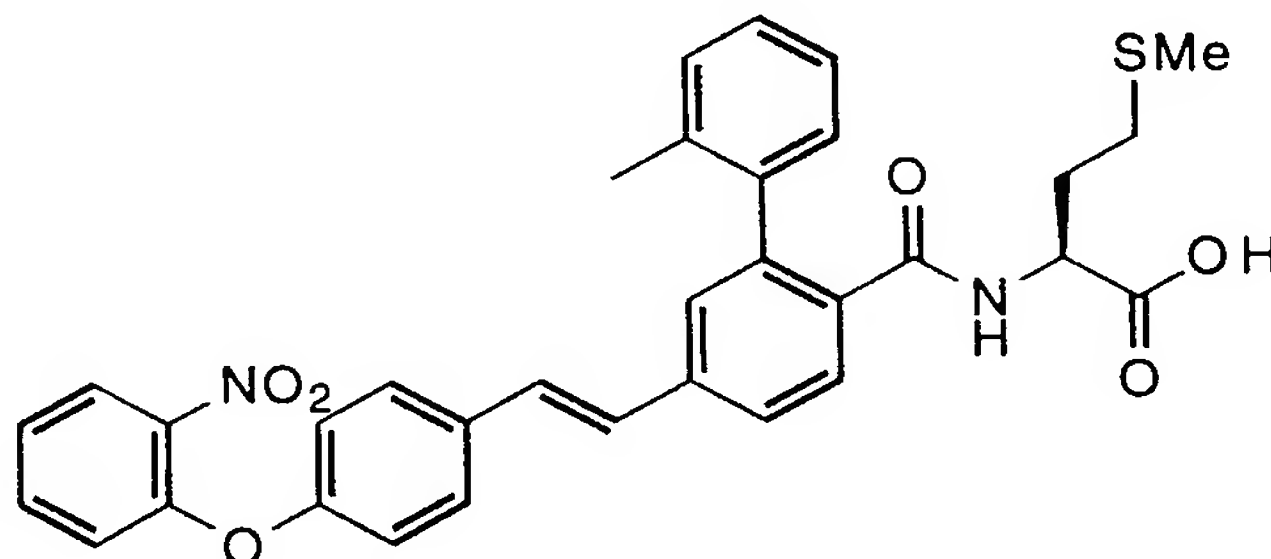
The desired compound was prepared according to the method of Examples 210 -211. MS m/e 570 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.58 (m, 1H), 1.95 (m, 1H), 2.1 (m, 8H), 4.59 (m, 1H), 5.91 (m, 1H), 6.91-7.62 (m, 16H), 8.03 (m, 1H).

7325

Example 855

N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

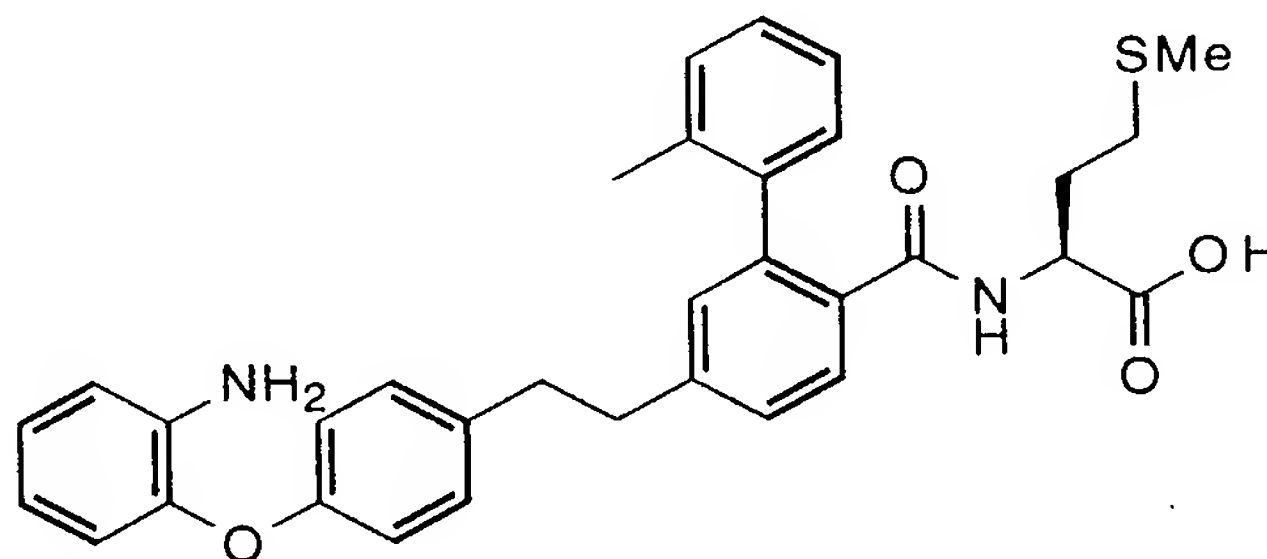
7330 The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 574 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.53 (m, 1H), 1.93 (m, 1H), 2.1 (m, 8H), 2.95 (m, 4H), 4.59 (m, 1H), 5.83 (m, 1H), 6.83-7.50 (m, 14H), 7.97 (m, 1H).

Example 856

7335

N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

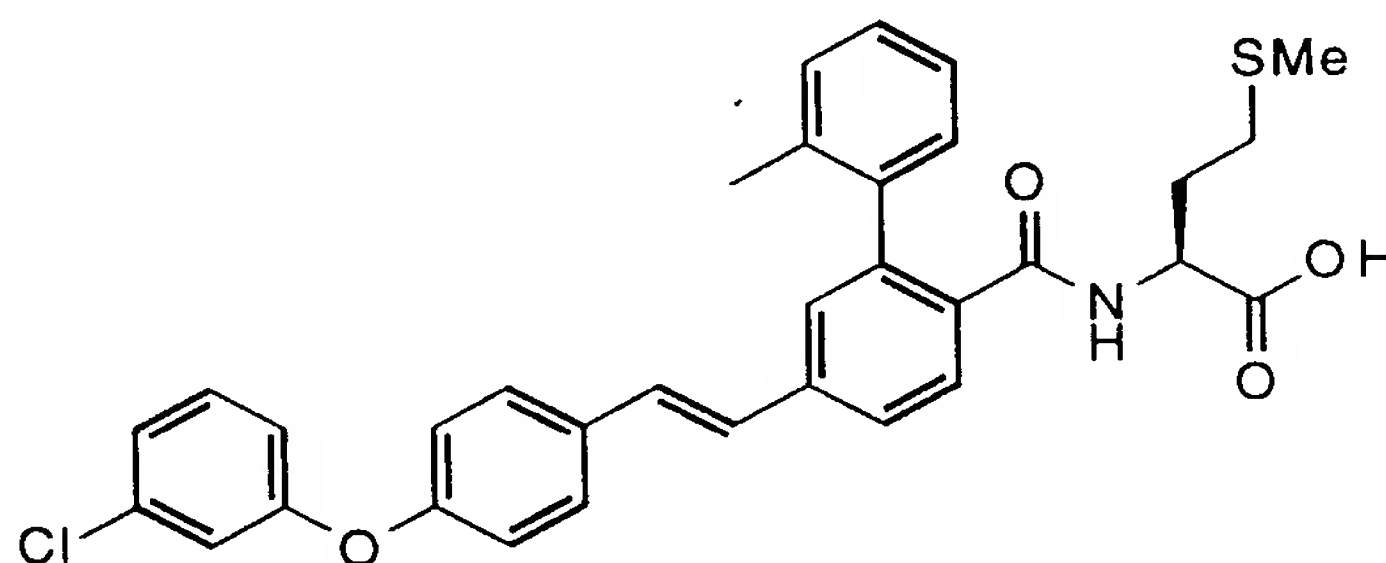
The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 583 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.57 (m, 1H), 1.93 (m, 1H), 2.1 (m, 8H), 4.58 (m, 1H), 5.90 (m, 1H), 6.65 (m, 2H), 6.90-7.50 (m, 14H), 7.96 (m, 1H).



Example 857

N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

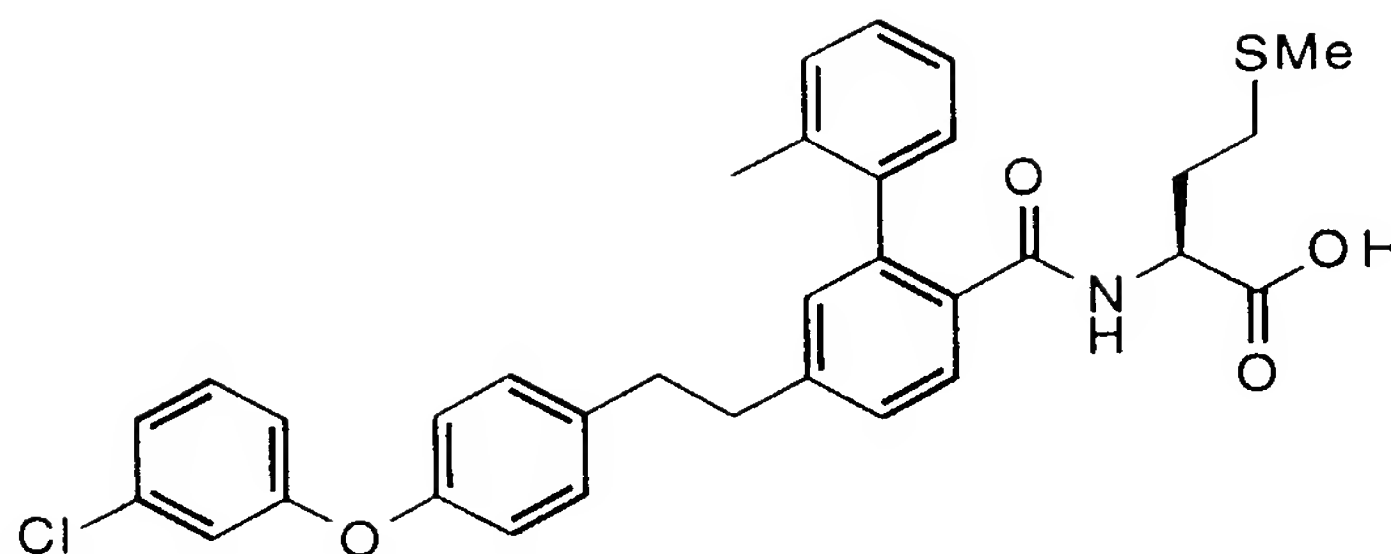
The title compound was prepared in an analogous manner Example 212 except that the final compound was extracted out of pH 7 buffer after the final hydrolysis. MS m/e 555 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.49 (m, 1H), 1.91 (m, 1H), 2.1 (m, 8H), 2.95 (m, 4H), 4.56 (m, 1H), 5.84 (m, 1H), 6.68-7.38 (m, 14H), 7.97 (m, 1H).



Example 858

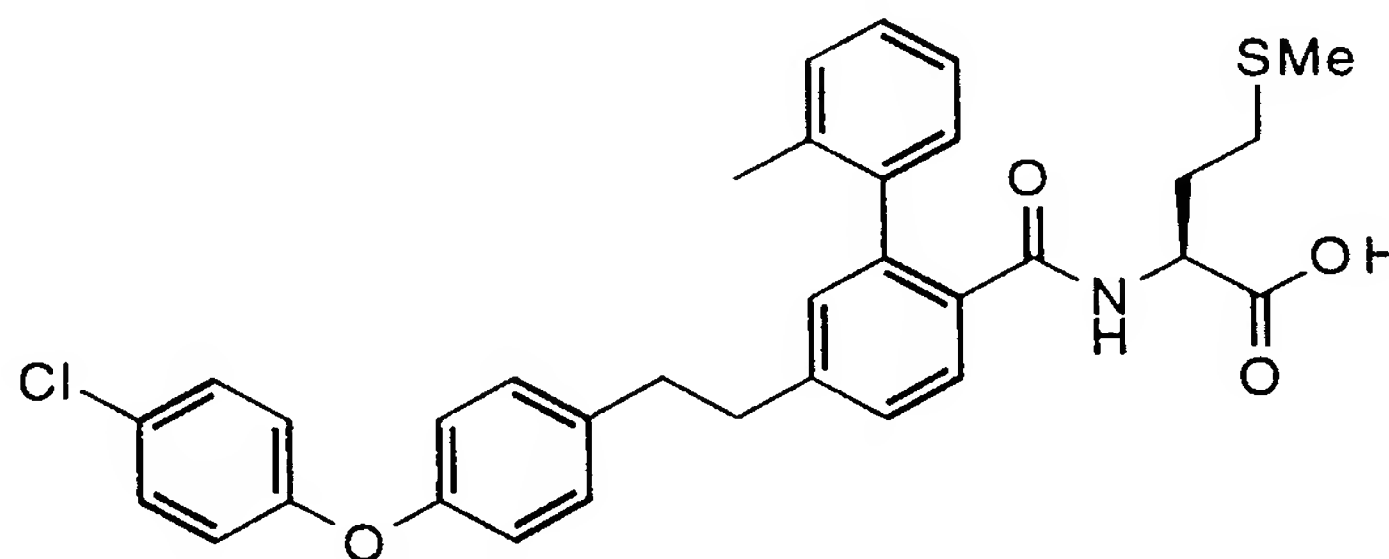
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 570 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.57 (m, 1H), 1.95 (m, 1H), 2.1 (m, 8H), 4.59 (m, 1H), 5.91 (m, 1H), 6.91-7.62 (m, 16H), 8.04 (m, 1H).

Example 859

N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

7365 The desired compound was prepared according to the method of Examples 210 -  
212. MS m/e 572 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.49 (m, 1H), 1.93 (m, 1H),  
2.1 (m, 8H), 2.97 (m, 4H), 4.55 (m, 1H), 5.84 (m, 1H), 6.81-7.37 (m, 14H), 7.98 (m,  
1H).

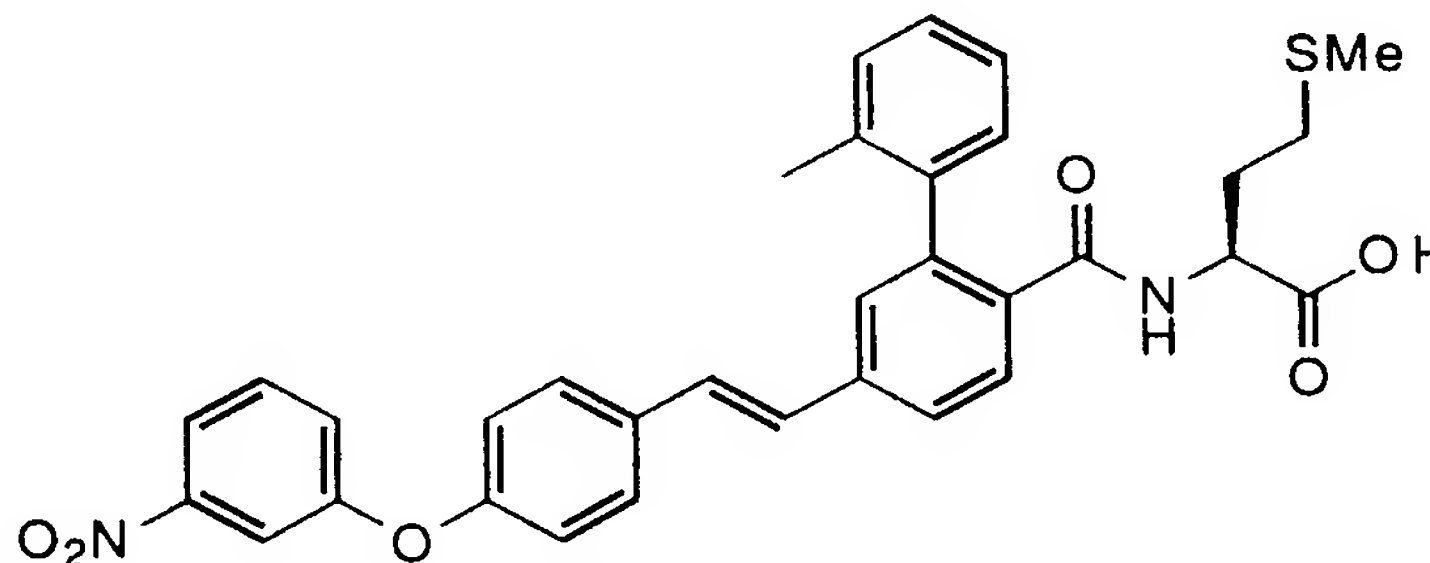


7370

Example 860

N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

7375 The desired compound was prepared according to the method of Examples 210 -  
212. MS m/e 574 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 300 MHz) δ 1.75 (m, 2H), 1.94 (m,  
6H), 2.06 (m, 2H), 2.94 (m, 4H), 4.13 (m, 1H), 6.92-7.48 (m, 12H), 7.66 (m, 2H), 7.97  
(m, 1H).



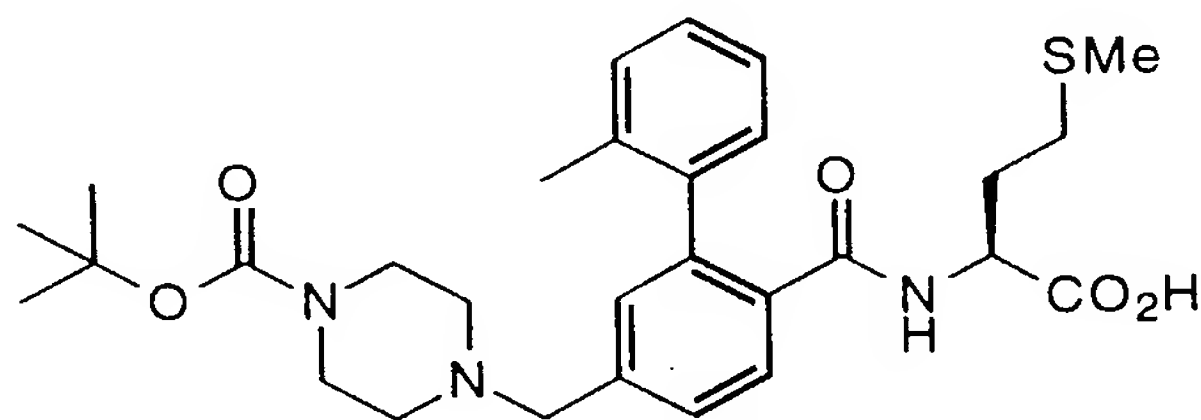
7380

Example 861

N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 583 (M+H)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.54 (m, 1H), 1.92 (m, 1H), 2.1 (m, 8H), 4.58 (m, 1H), 5.91 (m, 1H), 6.7-7.6 (m, 16H), 8.02 (m, 1H).

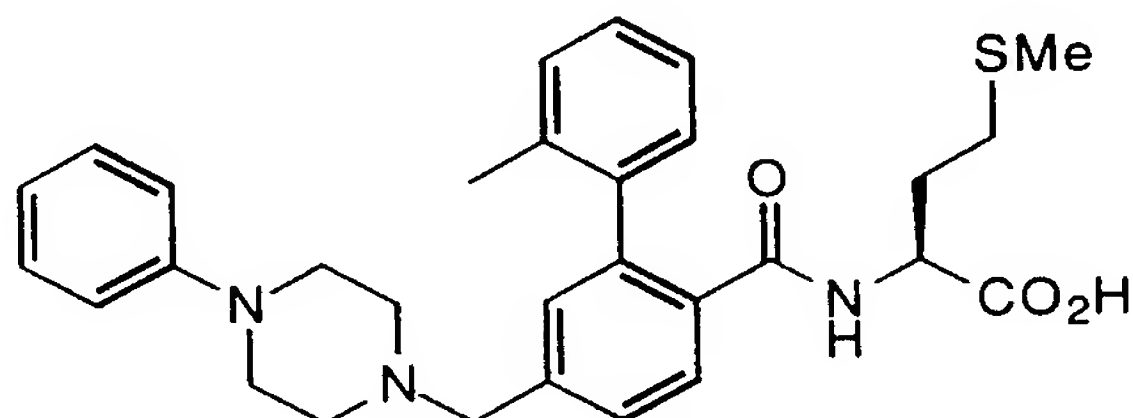
7385

Example 866N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7390

The desired compound was prepared according to the method of Example 158. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.45 (s, 9H), 1.60 (m, 1H), 1.82 (m, 1H), 2.05 (m, 8H), 2.53 (m, 4H), 3.46 (m, 4H), 3.62 (m, 2H), 4.38 (m, 1H), 6.00 (m, 1H), 7.10-7.50 (m, 6H), 7.86 (m, 1H). MS m/e 540 (M-H)<sup>-</sup>.

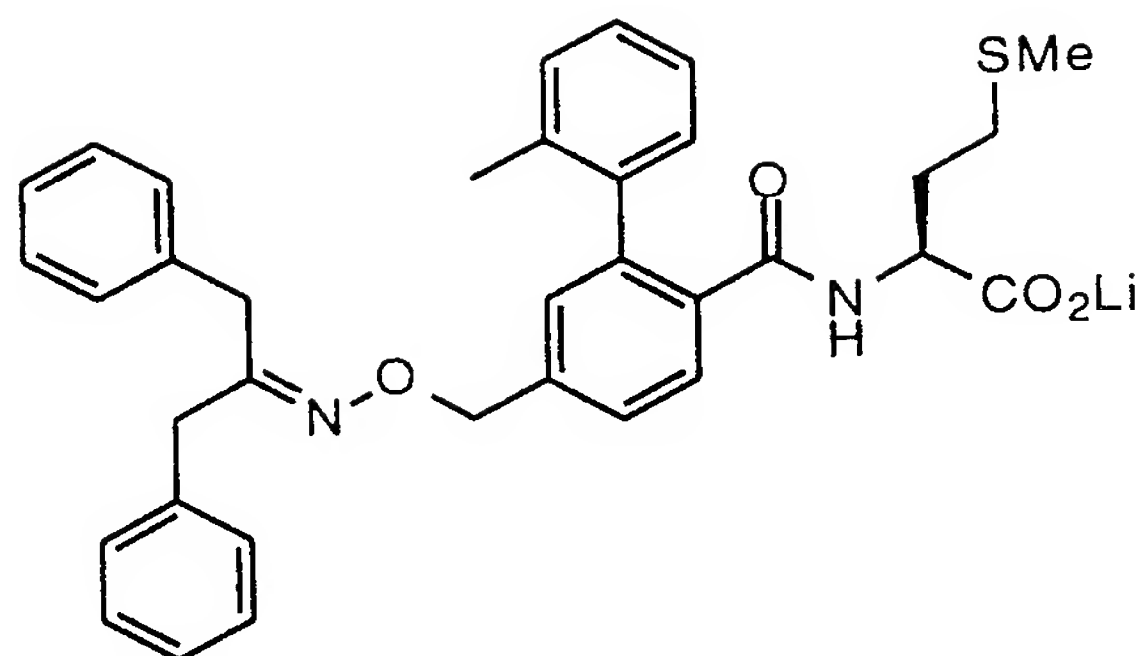
7395

Example 867N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7400

The desired compound was prepared according to the method of Example 158. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.47 (m, 1H), 1.82 (m, 1H), 2.0 (m, 8H), 2.75 (m, 4H), 3.21 (m, 4H), 3.65 (m, 2H), 4.30 (m, 1H), 6.11 (m, 1H), 6.89 (m, 2H), 7.22 (m, 8H), 7.40 (m, 1H), 7.82 (m, 1H). MS m/e 516 (M-H)<sup>-</sup>.



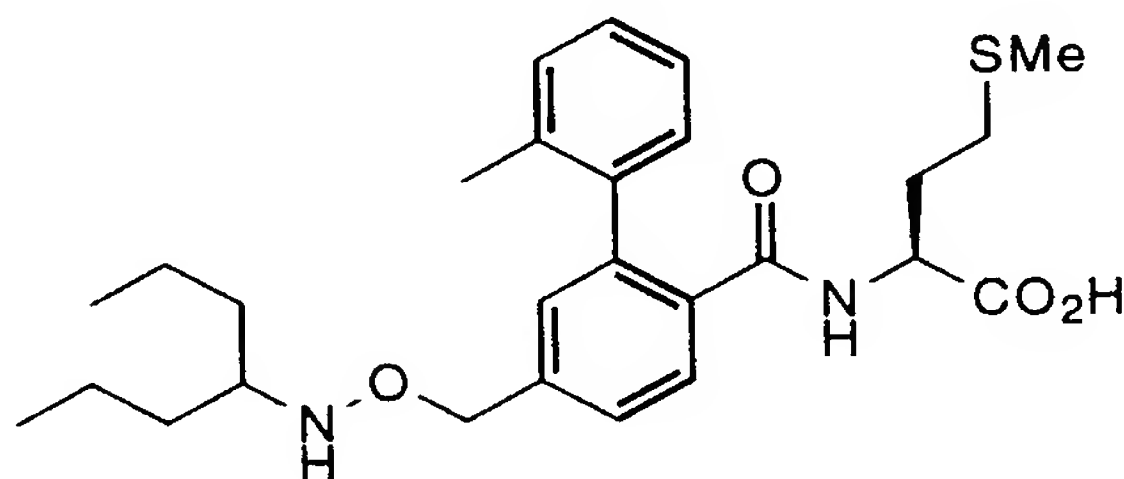


7405

Example 888N-[4-N-(1,3-Diphenylpropan-2-yl)iminooxymethyl]-2-(2-methylphenyl)benzoyl-methionine lithium salt

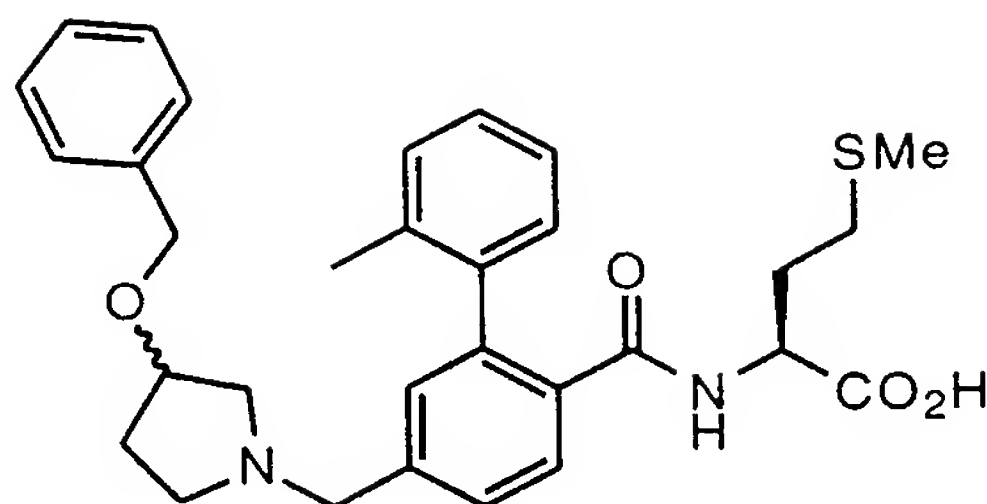
7410 The desired compound was prepared according to the method of Example 157. <sup>1</sup>H NMR (300 MHz, DMSO) δ 1.50-1.62 (m, 1H), 1.63-1.76 (m, 1H), 1.92 (s, 3H), 1.95-2.15 (m, 5H), 3.38 (s, 2H), 3.53 (s, 2H), 3.69 (brs, 1H), 5.18 (s, 2H), 6.98 (d, J=6.4 Hz, 1H), 7.04-7.28 (m, 15H), 7.36 (dd, J=7.8, 1.7 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H). MS (ESI) m/z 587 (M+H); Analysis calc'd for C<sub>35</sub>H<sub>35</sub>LiN<sub>2</sub>O<sub>4</sub>S•1.0H<sub>2</sub>O: C, 69.52; H, 6.17; N, 4.63; found: C, 69.47; H, 6.09; N, 4.58.

7415

Example 929N-[4-(N-Hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]methionine

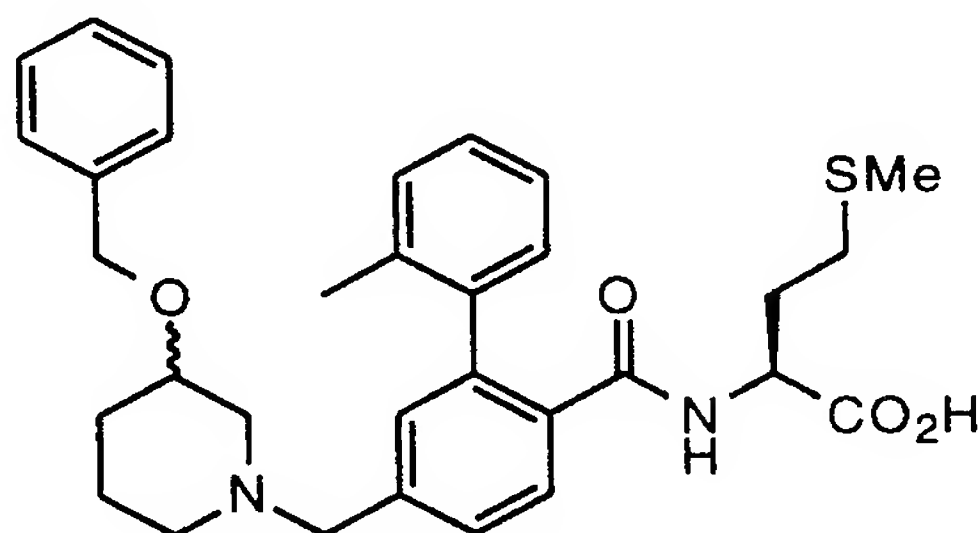
7420 The desired compound was prepared according to the method of Example 157. <sup>1</sup>H (300MHz, DMSO-d<sub>6</sub>, δ) 7.52 (1H, d, J=8Hz), 7.37 (1H, dd, J=9&2Hz), 7.30-7.10 (4H, m), 7.10 (1H, bs), 6.97 (1H, m), 6.33 (1H, bd, J=10Hz), 4.63 (2H, s), 3.68 (1H, m), 2.74 (1H, m), 2.20-1.95 (3H, m), 1.92 (3H, s), 1.90-1.40 (4H, m), 1.40-1.20 (8H, m), 0.83 (6H, t, J=8Hz). m/z (ESI) 485 (MH<sup>+</sup>) Anal.calc. for C<sub>27</sub>H<sub>37</sub>LiN<sub>2</sub>O<sub>4</sub>S•0.25 H<sub>2</sub>O C 65.24, H 7.60, N 5.64 Found C 65.14, H 7.81, N 5.33

7425

Example 988

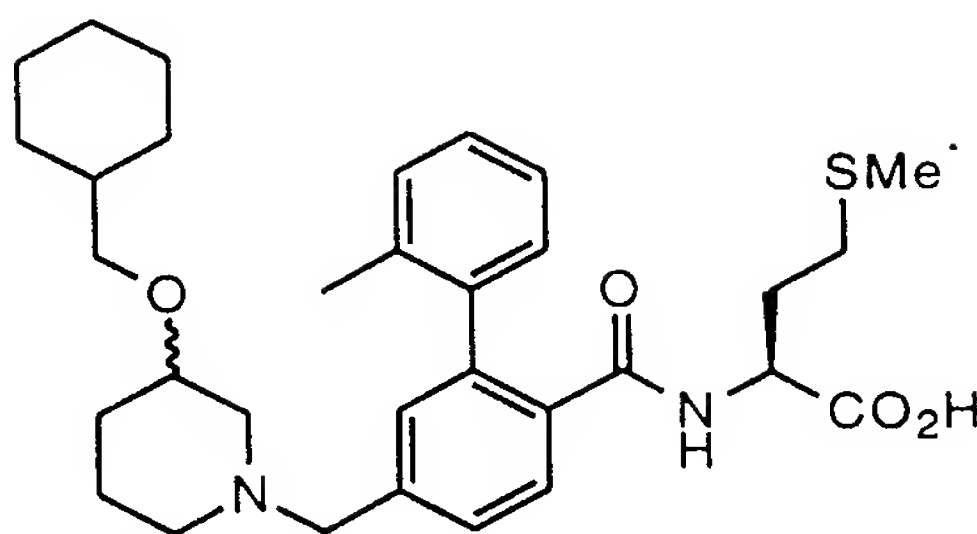
7430 N-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 <sup>1</sup>H nmr (300 MHz, DMSO d<sub>6</sub>): δ 8.08, d, 1H; 7.47, d, 1H; 7.37, dd, 1H; 7.29, m, 5H; 7.20, m, 2H; 7.14, m, 3H; 4.40, q (AA'), 2H; 4.21, m, 1H; 4.11, m, 1H; 3.68, q (AA'), 2H; 2.41 - 2.76, m, 4H; 1.98 - 2.23, m, 6H; 1.97, s, 3H; 1.64 - 1.93, m, 3H. MS (ESI(-)): 531 (M-H); (ESI(+)): 533. Calc'd for C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>S: C 69.90, H 6.81, N 5.26: Found: C 69.21, H 6.86, N 5.06

Example 989

7440 N-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

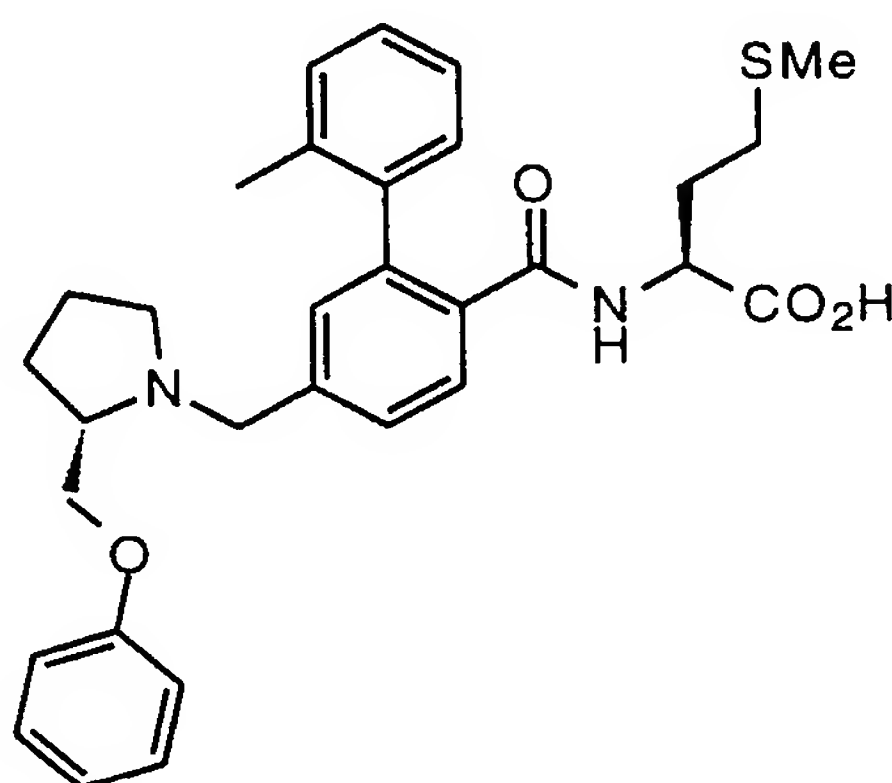
The desired compound was prepared according to the method of Example 158 <sup>1</sup>H nmr (300 MHz, DMSO d<sub>6</sub>): δ 8.09, d, 1H; 7.49, d, 1H; 7.37, dd, 1H; 7.23 - 7.34, m, 5H; 7.22, m, 2H; 7.12, m, 3H; 4.48, s, 2H; 4.23, ddd, 1H; 3.60, m, 2H; 3.46, m, 1H; 3.30, m, 2H; 2.95, m, 1H; 2.64, m, 1H; 2.00 - 2.24, m, 6H; 1.98, s, 3H; 1.63 - 1.96, m, 3H; 1.42, m, 1H; 1.22, m, 1H. MS (ESI(-)): 545 (M-H); (ESI(+)): 547. Calc'd for C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>S + 0.37 H<sub>2</sub>O: C 69.46, H 7.06, N 5.06: Found: C 69.45, H 7.14, N 4.76.



Example 990

N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

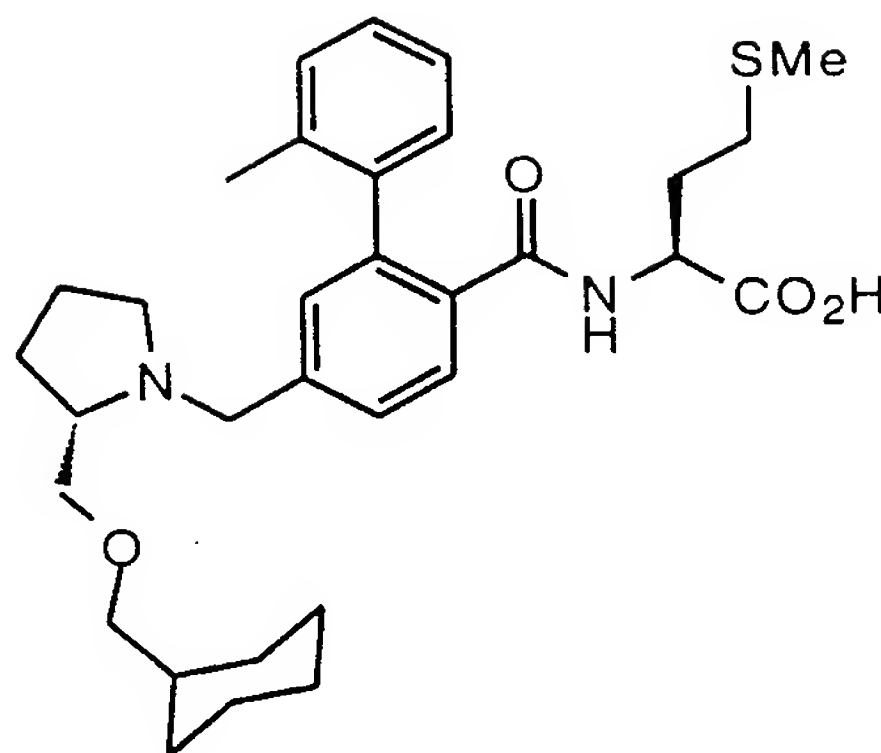
The desired compound was prepared according to the method of Example 158 <sup>1</sup>H nmr (300 MHz, DMSO d<sub>6</sub>): δ 7.98, d, 0.5H; 7.97, d, 0.5H; 7.37, d, 1H; 7.25, d, 1H; 7.09, m, 2H; 7.02, m, 3H; 4.10, m, 1H; 3.44, s, 2H; 3.15, m, 2H; 3.05, m, 2H; 2.77, m, 1H; 2.52, m, 1H; 1.88 - 2.13, m, 5H; 1.60 - 1.82, m, 3H; 1.51, m, 5H; H; 1.85, s, 3H; 1.30, m, 2H; 0.90 - 1.16, m, 4H; 0.75, m, 2H. MS (ESI(-)): 551 (M-H); (ESI(+)): 553. Calc'd for C<sub>32</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>S + 1.13 H<sub>2</sub>O: C 67.06, H 8.14, N 4.89: Found: C 67.06, H 7.88, N 4.80.



Example 991

N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 <sup>1</sup>H nmr (300 MHz, DMSO d<sub>6</sub>): δ 8.10, d, 1H; 7.48, d, 1H; 7.40, d, 1H; 7.01 - 7.30, m, 6H; 6.90, m, 3H; 4.22, m, 2H; 4.01, m, 1H; 3.85, m, 1H; 3.59, m, 1H; 3.34, m, 1H; 3.03, m, 1H; 2.91, m, 1H; 2.36, m, 1H; 1.98 - 2.24, m, 6H; 1.96, s, 3H; 1.60 - 1.90, m, 4H. MS (ESI(-)): 531 (M-H); (ESI(+)): 533. Calc'd for C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>S + 0.87 H<sub>2</sub>O: C 67.90, H 6.94, N 5.11: Found: C 67.90, H 6.95, N 4.87.

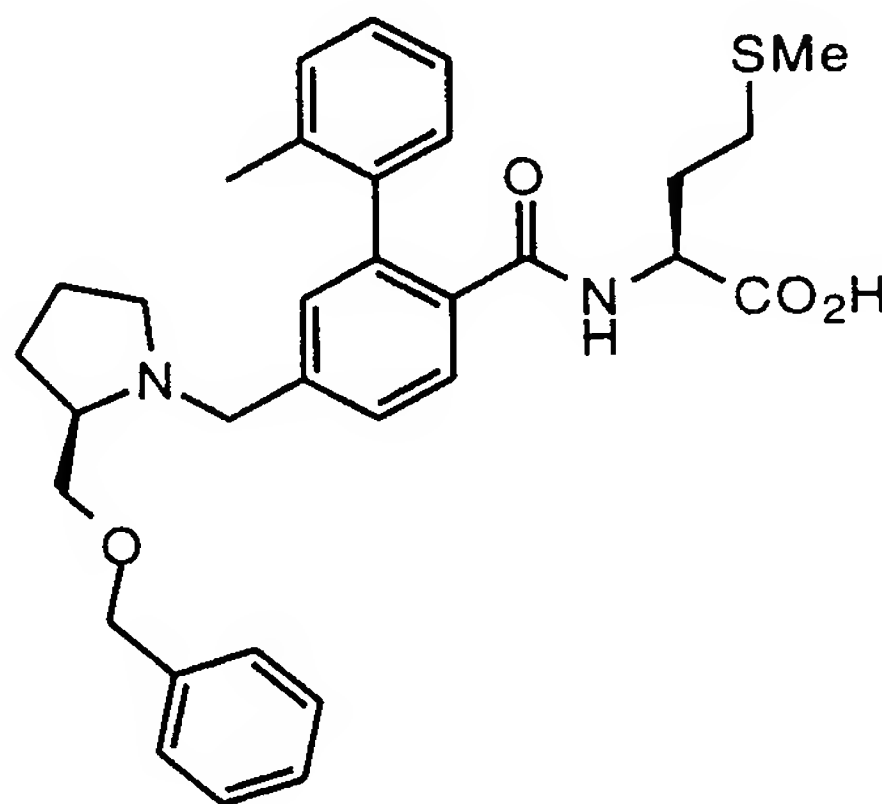
Example 992

7475 N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 <sup>1</sup>H nmr (300 MHz, DMSO d<sub>6</sub>): δ 8.11, d, 1H; 7.47, d, 1H; 7.38, d, 1H; 7.21, m, 2H;

7.16, m, 3H; 4.21, m, 2H; 3.53, m, 1H; 3.25 - 3.46, m, 3H; 3.18, dq (AA'), 2H; 2.87, m, 2H; 2.30, m, 1H; 1.99 - 2.24, m, 6H; 1.97, s, 3H; 1.77 - 1.95, m, 2H; 1.56 - 1.76, m, 6H; 1.40 - 1.55, m, 2H; 1.51, m, 3H; 0.88, m, 2H. MS (ESI(-)): 551 (M-H); (ESI(+)): 553. Calc'd for C<sub>32</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>S + 0.74 H<sub>2</sub>O: C 67.90, H 8.10, N 4.95: Found: C 67.89, H 7.83, N 4.79.

7485

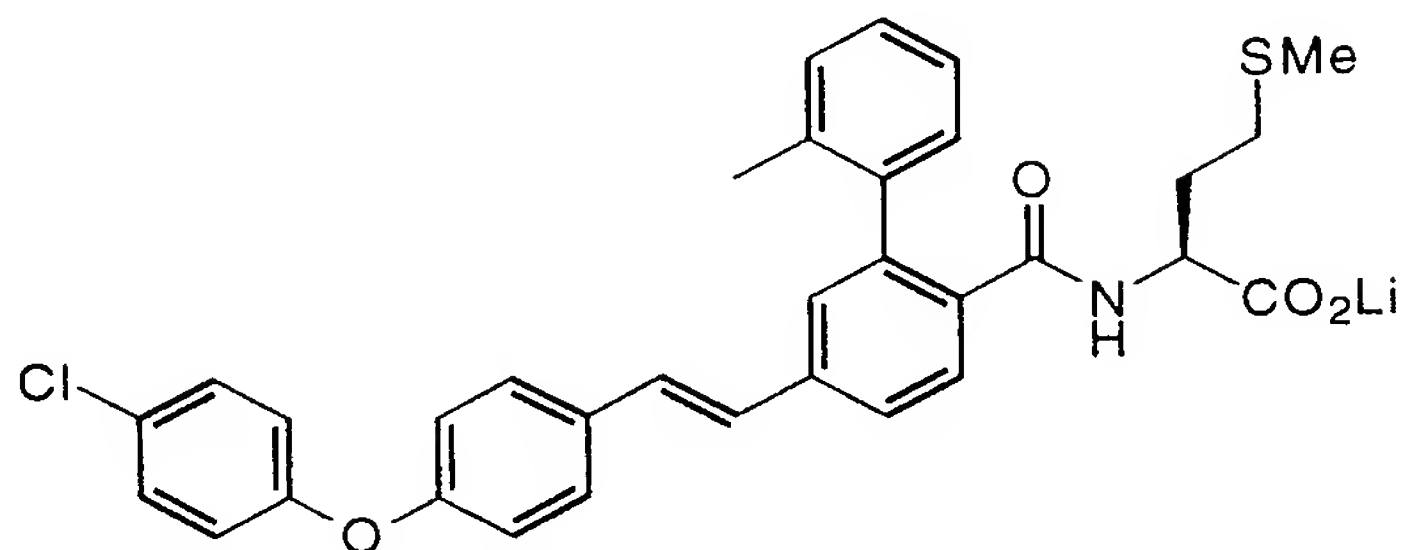
Example 993

N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7490 The desired compound was prepared according to the method of Example 158 <sup>1</sup>H nmr (300 MHz, DMSO d<sub>6</sub>): δ 8.12, d, 1H; 7.49, d, 1H; 7.39, d, 1H; 7.30, m, 5H; 7.21, m, 2H; 7.15, m, 3H; 4.48, s, 2H; 4.22, m, 2H; 3.53, m, 2H; 3.40, m, 2H; 2.89, m, 2H; 2.23 - 2.40, m, 1H; 2.00 - 2.22, m, 5H; 1.98, s, 3H; 1.50 - 1.94, m, 6H. MS (ESI(-)):

545 (M-H); (ESI(+)): 547. Calc'd for  $C_{32}H_{38}N_2O_4S + 1.60 H_2O$ : C 66.78, H 7.22, N 4.87; Found: C 66.79, H 6.88, N 4.70.

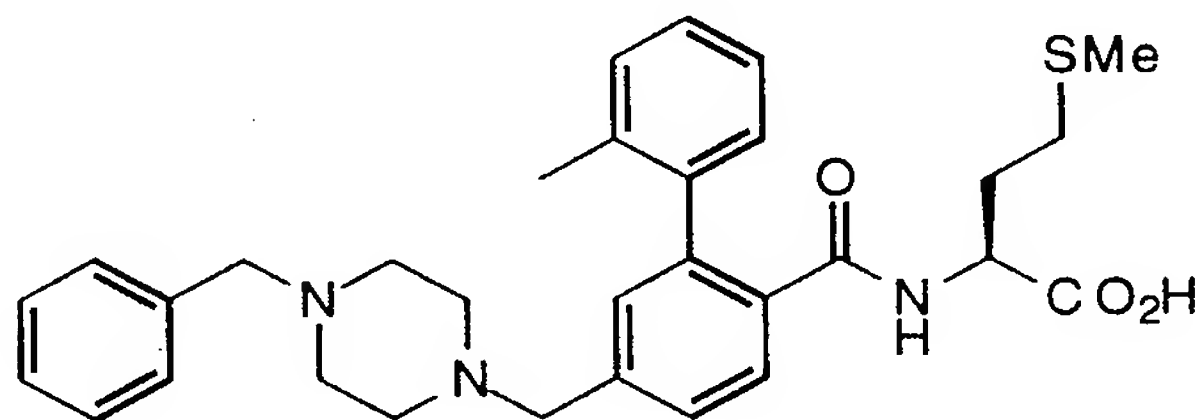
7495

Example 1016

7500 N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine  
lithium salt

Prepared as in Example 210. MS m/e 570 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 300 MHz) δ 1.5-2.2 (m, 10H), 3.65 (m, 1H), 6.95 (m, 1H), 7.02-7.69 (m, 17H).

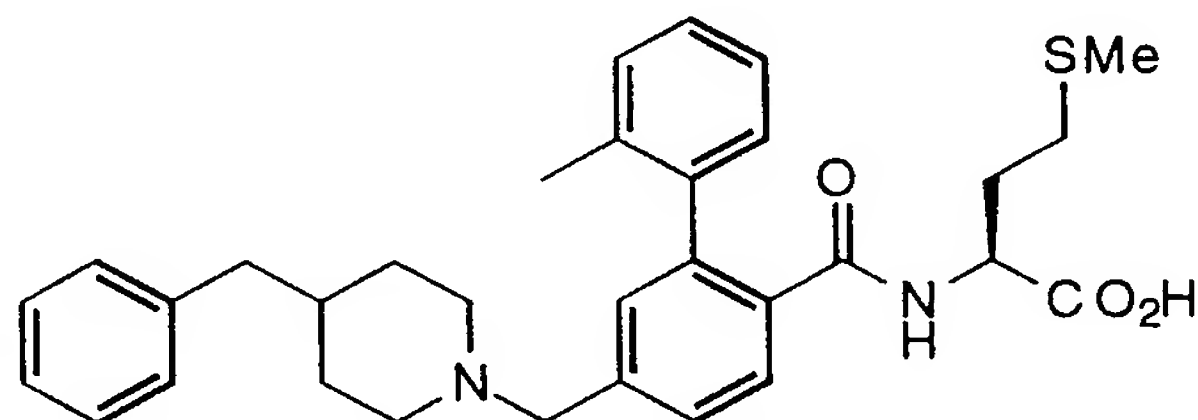
7505

Example 1035

N-[4-(4-benzylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared similarly. MS m/e 530 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.65 (m, 1H), 1.95 (m, 1H), 2.08 (m, 8H), 2.75 (m, 8H), 3.71 (m, 4H), 4.42 (m, 1H), 6.21 (m, 1H), 7.3 (m, 11H), 7.79 (m, 1H).

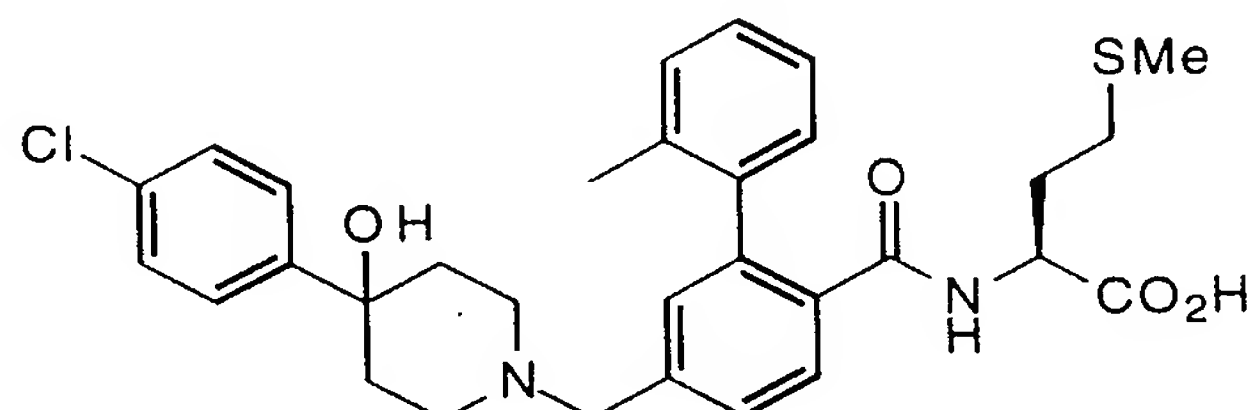
7510

Example 1036

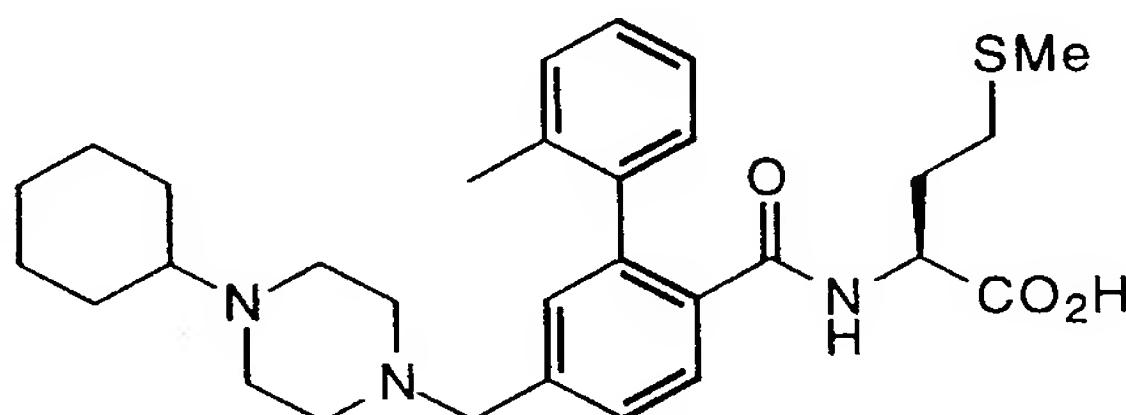
7515

N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

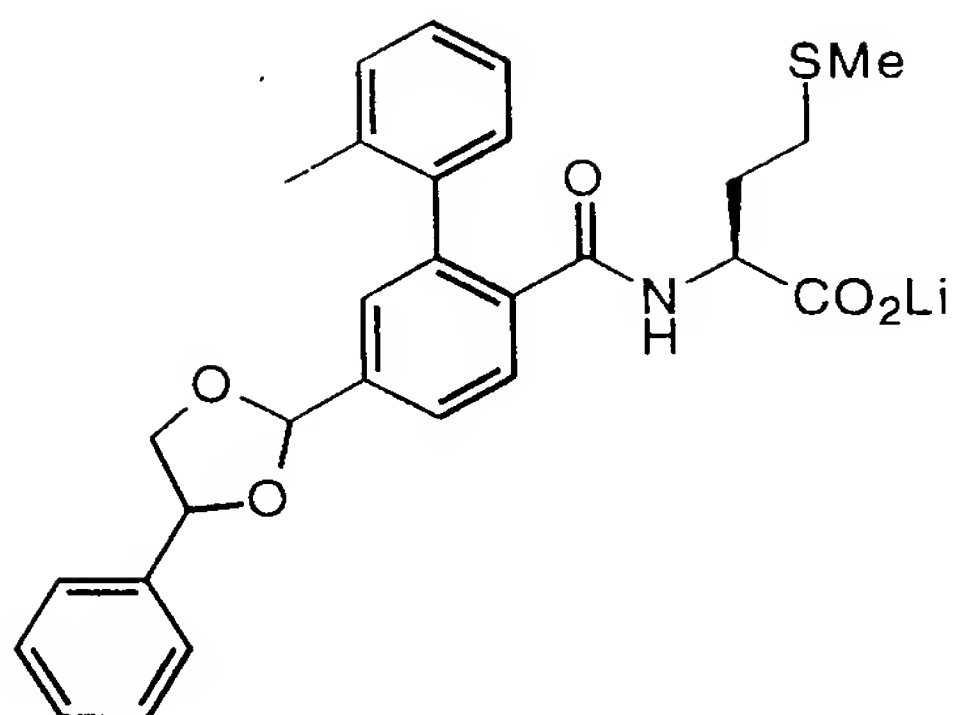
Prepared similarly. MS m/e 529 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.65 (m, 5H), 1.95 (m, 1H), 2.06 (m, 8H), 2.41 (m, 1H), 2.56 (m, 2H), 3.30 (m, 2H), 3.55 (m, 1H), 3.71 (m, 2H), 4.13 (m, 1H), 4.42 (m, 1H), 6.30 (m, 1H), 7.18 (m, 10H), 7.47 (m, 1H), 7.77 (m, 1H).

Example 1037N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

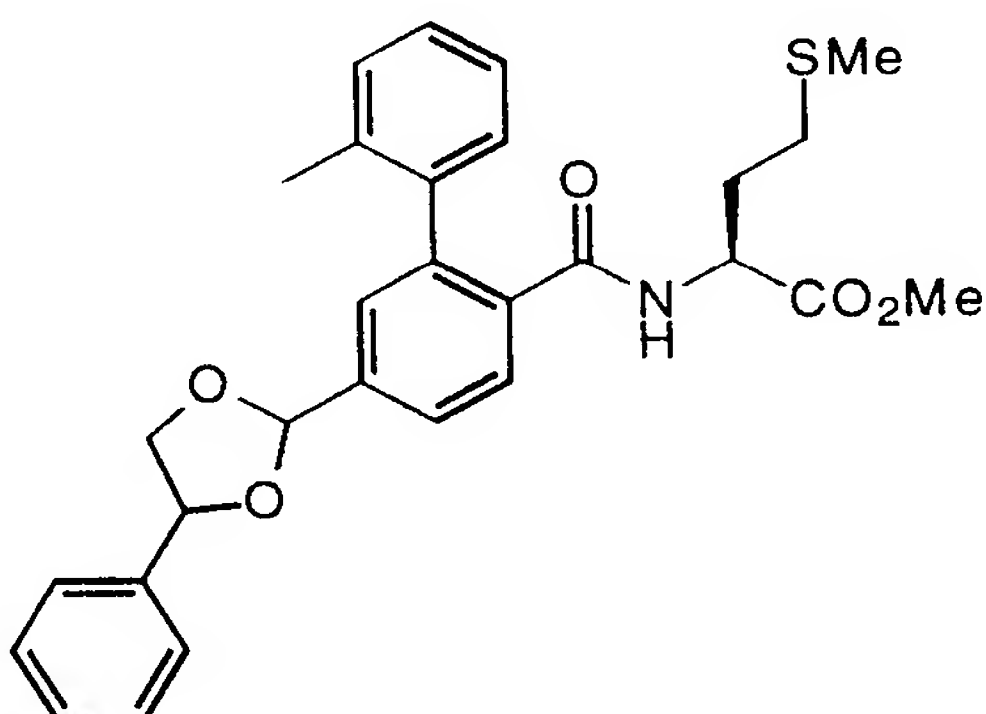
Prepared similarly. MS m/e 565 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, 300 MHz) δ 1.61 (m, 4H), 1.80 (m, 1H), 1.93 (m, 1H), 1.99 (s, 3H), 2.15 (m, 5H), 2.48 (m, 2H), 2.69 (m, 2H), 3.63 (s, 2H), 4.18 (m, 1H), 4.92 (s, 1H), 6.95 (m, 2H), 7.45 (m, 8H), 7.95 (m, 1H).

Example 1038N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared similarly. MS m/e 522 (M-H)<sup>-</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.29 (m, 6H), 1.68 (m, 1H), 1.88 (m, 5H), 2.05 (m, 8H), 2.71 (m, 4H), 2.89 (m, 1H), 3.58 (m, 6H), 4.38 (m, 1H), 6.42 (m, 1H), 7.2-7.5 (m, 6H), 7.74 (m, 1H).

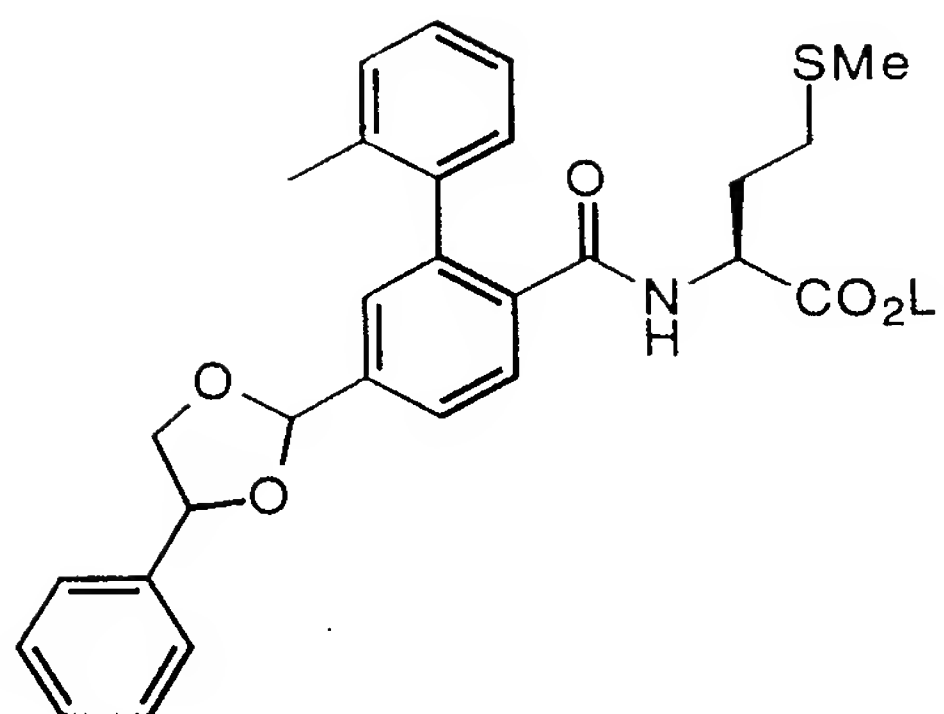
Example 1083

(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Lithium Salt

Example 1083A

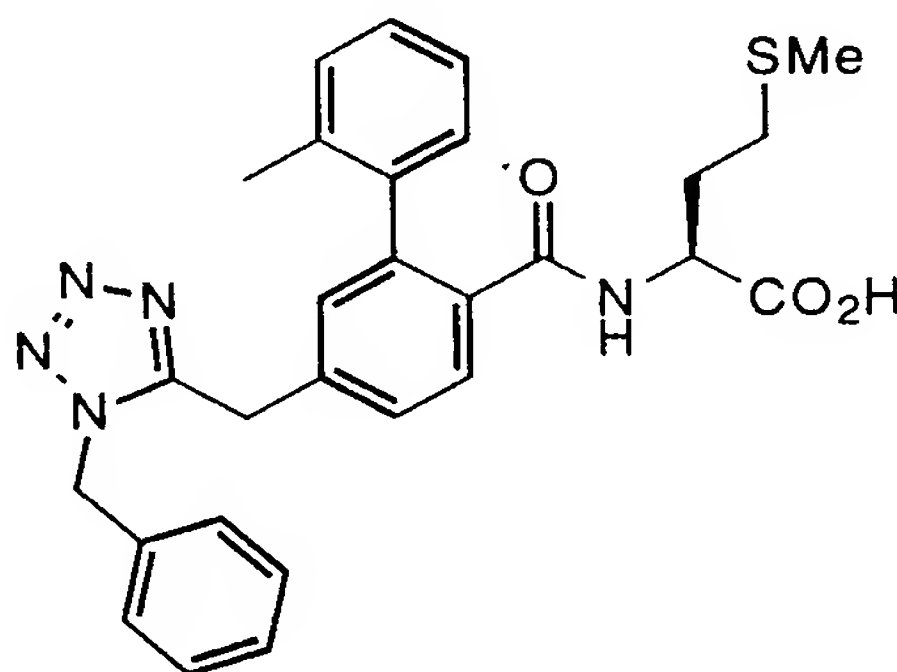
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

To a solution of N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 403G, 340mg) and 1,2-dihydroxyethylbenzene (134mg) in toluene (3mL) was added *p*-toluenesulfonic acid hydrate (17mg), and magnesium sulfate (212mg). After 7h at ambient temperature, the reaction was filtered through infusorial earth and concentrated. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexane to give the title compound as a colorless oil (330mg, 74%). MS (APCI(+)) *m/e* 506 (M+H)<sup>+</sup>. MS (APCI(-)) *m/e* 540 (M+Cl)<sup>-</sup>.

Example 1083B

(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Lithium Salt

7560 The title compound was prepared from (2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine methyl ester according to the procedure in example 608E, and was isolated as a white powder. <sup>1</sup>H NMR (300 MHz, DMSO) δ 1.51-1.88 (m, 4H), 1.92 (s, 3H), 1.98-2.20 (m, 3H), 3.62-3.73 (m, 1H), 3.76 (t, J=7.8 Hz, 0.5H), 3.85 (t, J=7.2 Hz, 0.5H), 4.38 (t, J=7.2 Hz, 0.5H), 4.56 (ddd, J=8.4, 6.6, 1.8 Hz, 0.5H), 5.25  
7565 (t, J=6.9 Hz, 1H), 6.20 (s, 0.5H), 6.22 (s, 0.5H), 7.00-7.12 (m, 1H), 7.25-7.47 (m, 10H), 7.59 (d, J=6 Hz, 2H). MS (APCI(+)) m/e 492 (M+H); Analysis calc'd for C<sub>28</sub>H<sub>28</sub>LiNO<sub>5</sub>S•1.30H<sub>2</sub>O: C, 64.56; H, 5.92; N, 2.69; found: C, 64.56; H, 5.69; N, 2.54



7570

Example 1099

N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7575

Step 1: 4-nitrilemethyl-2-(2-methylphenyl)phenylacetate

A 100 mL round-bottom flask was charged with 4-bromomethyl-2-(2-methylphenyl)phenylacetate (798.0 mg, 2.5 mmol and MeOH (23 mL)/ H<sub>2</sub>O (2 mL). Potassium cyanide (489.4 mg, 7.5 mmol) was added and allowed to stir at room



temperature for 12 h, then heated to reflux for 1 h, monitoring by TLC (1:1 EtOAc/hexane).

7580 The reaction was cooled and solvent was removed under vacuum. It was then diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The product was purified by silica gel column (1:1 EtOAc/Hexane). Yield: 597.3 mg (90%), off-white solid. <sup>1</sup>H NMR (δ, CDCl<sub>3</sub>): 8.0 (2H), 7.0-7.5 (5H), 2.83 (2H), 3.6 (3H), 2.05 (3H), 1.55 (1H).  
7585 Mass spec(ESI): 266 (M+1), 264 (M-1).

Step 2: 4-tetrazol-5-ylmethyl-2-(2-methylphenyl)phenylacetate

A 100 mL 3-neck round-bottom flask was charged with 4-nitrilemethyl-2-(2-methylphenyl)phenylacetate (533.3 mg, 2 mmol) and dmf (25 mL) under N<sub>2</sub> purge.

7590 Sodium azide (910.1 mg, 12 mmol) and triethylamine hydrochloride (1.3780 g, 10 mmol) were added. The reaction was heated at 100 °C for 48 h. After cooling, 1 M NaHCO<sub>3</sub> (50 mL) was added. The reaction was extracted with Et<sub>2</sub>O (3 x 25 mL). The aqueous layer was acidified with 1 M H<sub>3</sub>PO<sub>4</sub> to pH = 3. Then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over  
7595 MgSO<sub>4</sub>, filtered and concentrated under vacuum. The product was purified by silica gel column (CHCl<sub>3</sub>/MeOH/HOAc (95:5:1)). Yield: 691.2 mg, yellow oil. Mass spec(ESI): 309 (M+1), 307 (M-1).

Step 3: 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (A) and 4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (B)

7600

A 25 mL round-bottom flask was charged with 4-tetrazol-5-ylmethyl-2-(2-methylphenyl)phenylacetate (618.1 mg, 2 mmol) in CH<sub>3</sub>CN (9.5 mL)/water (0.5 mL). Benzyl bromide (0.36 mL, 3 mmol) and potassium hydrogen carbonate (1 g) were added. The reaction was stirred for 4 h and then diluted with water. The mixture was extracted  
7605 with Et<sub>2</sub>O (3 x 10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The two regioisomers were separated by silica gel column (40% EtOAc/Hexane). Yield: 255.7 mg (product A) and 277.6 mg (product B). Product A: <sup>1</sup>H NMR (δ, CDCl<sub>3</sub>): 7.9 (2H), 7.0-7.4 (10H), 5.7 (2H), 4.27 (2H), 3.6 (3H), 2.0 (3H). Mass spec(ESI): 399 (M+1), 397 (M-1).  
7610 Product B: <sup>1</sup>H NMR (δ, CDCl<sub>3</sub>): 7.9 (2H), 6.9-7.4 (10H), 5.4 (2H), 4.2 (2H), 3.6 (3H), 2.0 (3H). Mass spec(ESI): 399 (M+1), 397 (M-1).

Step 4: 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoic acid

7615 A 50 mL round-bottom flask was charged with 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (A) (205.8 mg, 0.52 mmol) and ethanol (10 mL). 4 N sodium hydroxide (1.1 mL, 4.16 mmol) was added. The reaction was refluxed for 2 h and then cooled. The solvent was removed under vacuum and then diluted with water. The reaction was extracted with Et<sub>2</sub>O (3 x 10 mL). The pH of the aqueous layer was adjusted to 2 with 1 M H<sub>3</sub>PO<sub>4</sub>. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined  
7620 organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. Yield: 205.1 mg, white solid. <sup>1</sup>H NMR (δ, CDCl<sub>3</sub>): 8.0 (2H), 7.0-7.4 (10H), 5.7 (2H), 4.3 (2H), 2.0 (3H).

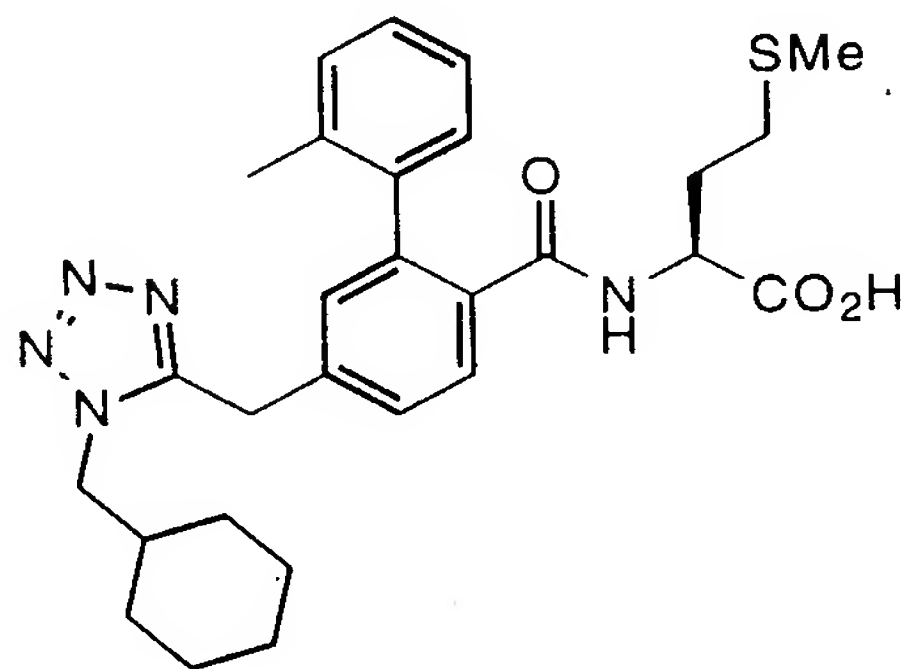
Step 5: N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7625 A 50 mL round-bottom flask was charged with 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoic acid (205.1 mg, 0.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) (110.1 mg, 0.572 mmol), L-methionine methyl ester hydrochloride (135.0 mg, 0.676 mmol), 1-hydroxybenzotriazole (78.6 mg, 0.572 mmol) and dmf (3 mL). The reagents were stirred until completely dissolved and then  
7630 triethylamine (0.14 mL, 0.936 mmol) was added. The reaction was stirred about 48 h until no starting material was present. Water (2 mL) and EtOAc (2 mL) were added to dissolve the precipitate. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 2 M Na<sub>2</sub>CO<sub>3</sub> (10 mL), water (10 mL) and brine (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. Yield: 273.0 mg, yellow solid. <sup>1</sup>H  
7635 NMR (δ, CDCl<sub>3</sub>): 8.0 (2H), 7.0-7.4 (10H), 5.85 (1H), 5.7 (2H), 4.6 (1H), 4.3 (2H), 3.65 (3H), 1.95-2.2 (6H), 1.5-1.9 (4H).

Step 6: N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine-carboxylic acid

7640 A 25 mL round-bottom flask was charged with N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine (273.0 mg, 0.53 mmol) and 3 mL of MeOH/THF (1:1). The flask was cooled to 0°C and 1 M lithium hydroxide (1.1 mL, 1.07 mmol) was added. The bath was removed and the reaction stirred for about 3 h, monitoring by TLC (1:1 EtOAc/Hexane). The solvent was removed under vacuum and the reaction diluted with  
7645 water. The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. Yield: 176.2 mg yellow solid.  
<sup>1</sup>H NMR (δ, CDCl<sub>3</sub>): 7.9 (2H), 7.0-7.4 (10H), 5.9 (1H), 5.7 (2H), 4.57 (1H), 4.3 (2H), 2.0-2.2 (6H), 1.9 (2H), 1.5 (2H)

7650 Mass spec (ESI): 516 (M+1), 514 (M-1)  $C_{28}H_{29}N_5O_3S \cdot 1.30 H_2O$   
 Anal. Calc'd.: C 62.39 H 5.91 N 12.99. Found: C 62.43 H 5.64 N 12.83



7655

Example 1100

N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Procedure: Follow example 1102 (product B). Yield: 105.7 mg, pale yellow solid.

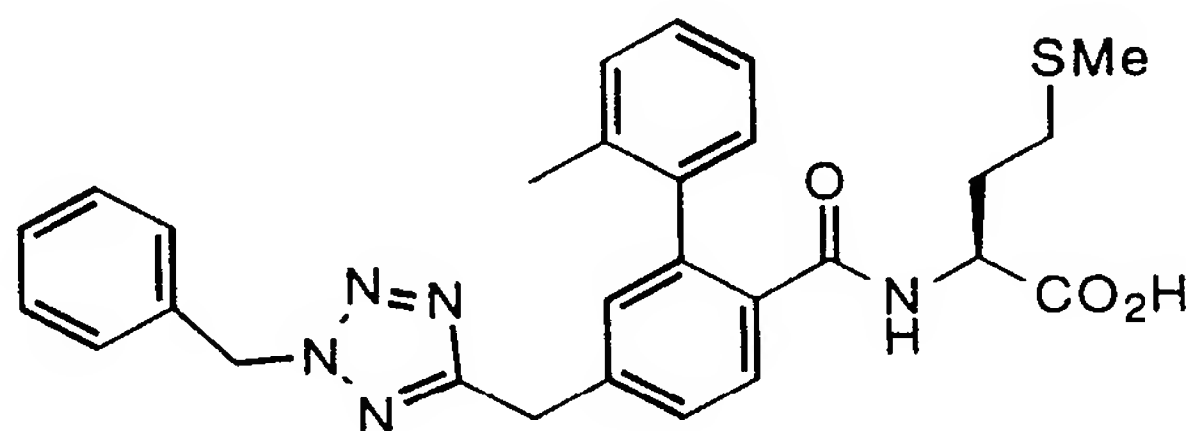
N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine.

$^1H$  NMR ( $\delta$ ,  $CDCl_3$ ): 7.95 (1H), 7.0-7.4 (5H), 5.9 (1H), 4.55 (1H), 4.3 (2H), 4.0 (2H),  
 2.9 (3H), 0.8-2.2 (20H)

7660

Mass spec (ESI): 522 (M+1), 520 (M-1)  $C_{28}H_{35}N_5O_3S \cdot 0.90 H_2O \cdot 0.05 CH_3CN$

Anal Calc'd.: C 62.51 H 6.90 N 13.10 Found: C 62.51 H 6.43 N 12.92



7665

Example 1101

N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Procedure: Follow example 1099 (product B). Yield: 176.2 mg.

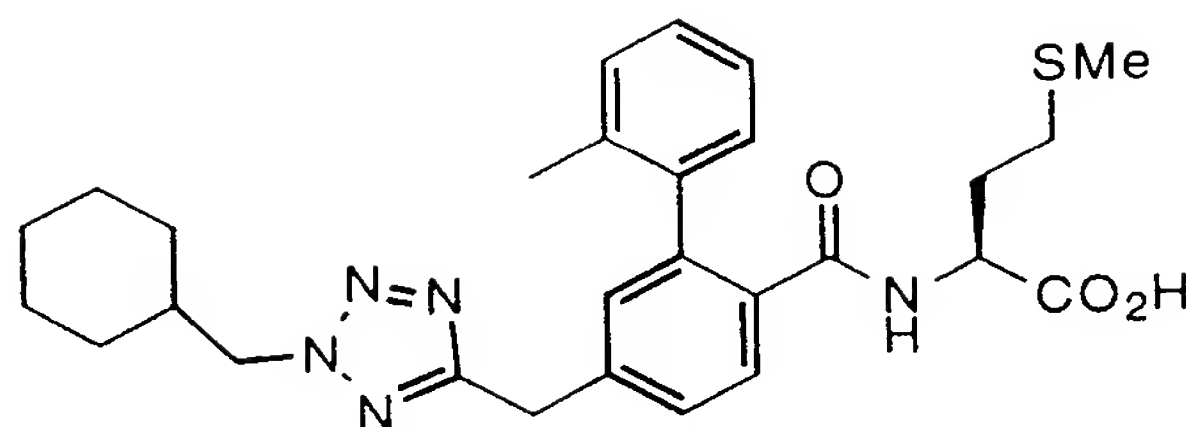
7670 N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine.

$^1H$  NMR ( $\delta$ ,  $CDCl_3$ ): 7.92 (2H), 6.8-7.4 (10H), 5.9 (1H), 5.4 (2H), 4.55 (1H), 4.2 (2H),  
 2.0-2.2 (6H), 1.9 (2H), 1.55 (2H)

Mass spec (ESI): 516 (M+1), 514 (M-1)  $C_{28}H_{29}N_5O_3S \cdot 1.30 H_2O$

Anal. calc'd.: C 62.39 H 5.91 N 12.99 Found: C 62.43 H 5.65 N 12.53

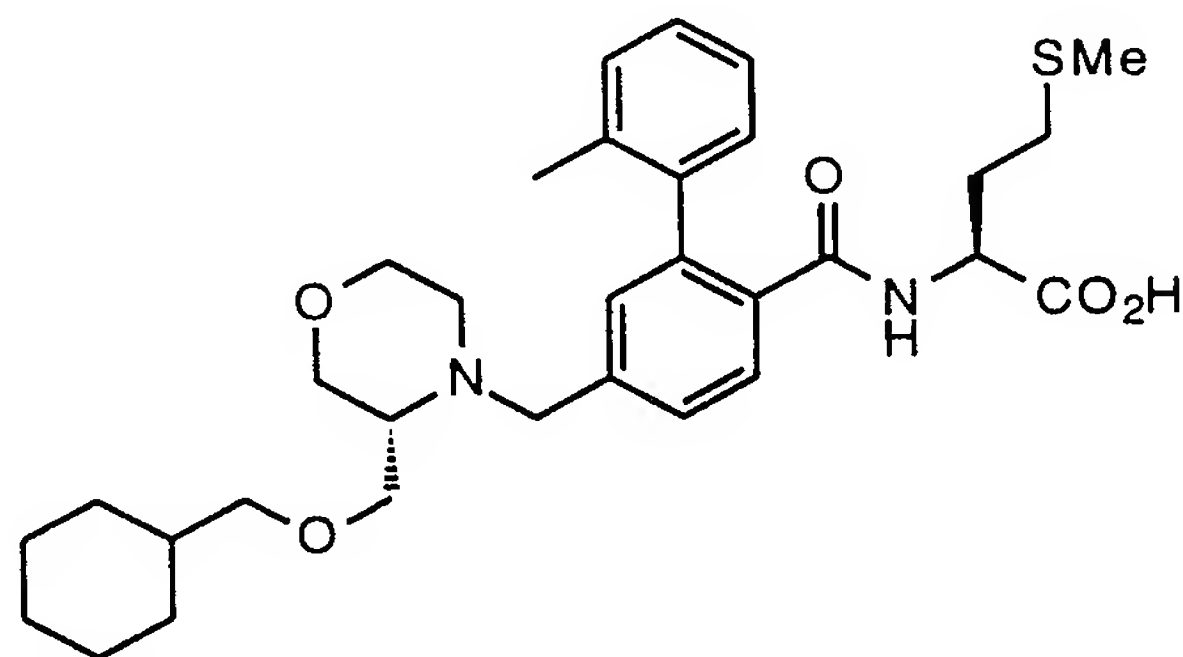
7675

Example 1102

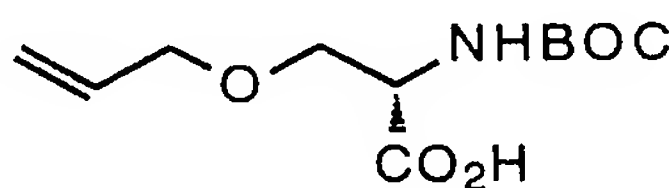
N-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7680 Procedure: Follow example 1099, except use bromomethylcyclohexane instead of benzylbromide (product A). Yield: 220.2 mg, pale yellow solid. N-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine  
<sup>1</sup>H NMR (δ, CDCl<sub>3</sub>): 7.95 (1H), 7.0-7.5 (5H), 5.9 (1H), 4.55 (1H), 4.4 (2H), 4.3 (2H), 2.9 (3H), 0.9-2.2 (20H)

7685 Mass spec (ESI): 522 (M+1), 520 (M-1) C<sub>28</sub>H<sub>35</sub>N<sub>5</sub>O<sub>3</sub>S•0.50H<sub>2</sub>O  
 Anal. Calc'd.: C 63.37 H 6.84 N 13.20 Found: C 63.58 H 6.54 N 12.80

Example 1109

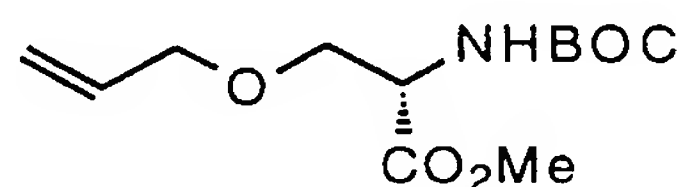
N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Example 1109A

O-Allyl-N-t-butoxycarbonyl-L-serine

7695 Serine (5.13 g, 25.0 mmol) in 60 mL of DMF was cooled in an ice bath and treated with sodium hydride (60%, 3.30 g, 82.5 mmol) in 3 portions over ~ 15 minutes and the mixture stirred until the cessation of bubbling (~20 minutes). The mixture was treated with allyl bromide (2.4 mL, 27.5 mmol) and after 5 minutes, the ice bath was removed. The

7705 mixture was stirred for 1.5 hours at ambient temperature and then quenched by the careful addition of water. The pH of the solution was adjusted to 2 with 1M aqueous phosphoric acid and extracted with 3 portions of ethyl acetate. The combined organic fractions were extracted with 3-30 mL portions of 1N aqueous sodium hydroxide and the combined aqueous phases washed with ether. The pH of the aqueous phase was adjusted to 2 with 1M aqueous phosphoric acid and extracted with 3 portions of ethyl acetate. The combined organic fractions were washed with water and brine, dried, filtered and concentrated to provide 6.10 g (99%) of the title compound. MS (DCI, NH<sub>3</sub>): 246 (MH<sup>+</sup>); 263 (M+NH<sub>4</sub>)<sup>+</sup>.

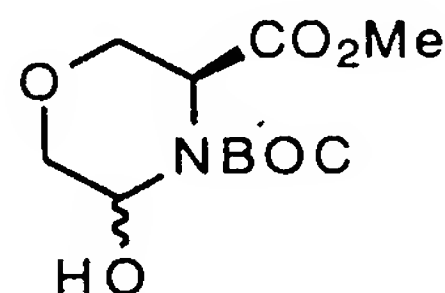


7710

Example 1109BO-Allyl-N-t-butoxycarbonyl-L-serine, methyl ester

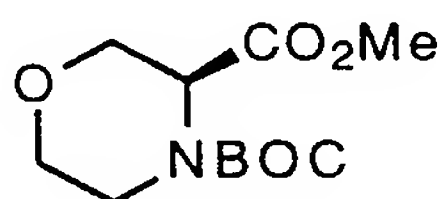
7715 A solution of example 1109A (6.09 g, 24.8 mmol) in 30 mL of 50% aqueous DMF was treated with cesium carbonate (8.09, 24.8 mmol) and the mixture stirred 30 minutes. Methyl iodide (3.1 mL, 49.7 mmol) was added and the mixture stirred for 60 hours at ambient temperature. The mixture was diluted with water and extracted with 3 portions of ethyl ether. The combined organic extracts were washed with water, 1N aqueous sodium hydroxide and brine, dried filtered and concentrated to provide 1.51 g (23%) of the title compound. MS (DCI, NH<sub>3</sub>): 260 (MH<sup>+</sup>); 277 (M+NH<sub>4</sub>)<sup>+</sup>.

7720

Example 1109C3(S)-Methoxycarbonyl-4-t-butoxycarbonyl-5-hydroxymorpholine

7725 Ozone was passed through a solution of example 1109B (1.50 g, 5.8 mmol) in 20 mL of 1:1 methanol/methylene chloride cooled in a dry ice/acetone bath until the solution turned blue. Nitrogen was passed through the cold solution until the blue color was discharged and then dimethyl sulfide (3 mL) was added and the cooling bath removed and the mixture stirred overnight and concentrated. The residue was dissolved in ether and washed with water, brine, dried, filtered and concentrated to provide 1.5 g of the title compound that was used directly.

7730



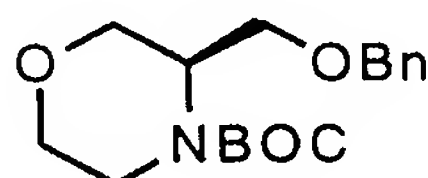


Example 1109D3(S)-Methoxycarbonyl-4-t-butoxycarbonylmorpholine

7735 A solution of example 1109C (522 mg, 2.0 mmol) in 4 mL of methylene chloride was cooled in an ice/acetone bath and triethylsilane (1.6 mL, 10.0 mmol) was added. The solution was then treated with a solution of boron trifluoride etherate (0.27 mL, 2.2 mmol) in 1 mL of methylene chloride. After stirring 30 minutes, the bath was removed and stirring continued for 30 minutes and the mixture was quenched by the addition of 2M aqueous  
7740 sodium carbonate. The mixture was diluted with water and methylene chloride and the layers separated. The aqueous layer was extracted with 2 portions of methylene chloride and the combined organic layers were dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (40 g, 20% ethyl acetate/hexanes) to provide 200 mg (41%) of the title compound. MS (DCI, NH<sub>3</sub>): 246 (MH<sup>+</sup>); 263  
7745 (M+NH<sub>4</sub>)<sup>+</sup>.

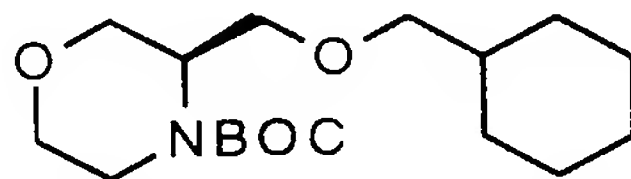
Example 1109E3(S)-Hydroxymethyl-4-t-butoxycarbonylmorpholine

7750 A solution of example 1109D (376 mg, 1.53 mmol) in 4 mL of ethanol was treated with calcium chloride (310 mg, 3.06 mmol) and the mixture stirred until a clear solution resulted. The solution was diluted with 2 mL of THF and then treated with sodium borohydride (232 mg, 6.13 mmol) and the mixture stirred for 4 hours. The reaction was quenched by the addition of water, diluted with 2M aqueous sodium carbonate and extracted  
7755 with 3 portions of methylene chloride. The combined organic fractions were dried, filtered and concentrated to provide 268 mg (83%) of the title compound. MS (DCI, NH<sub>3</sub>): 218 (MH<sup>+</sup>); 235 (M+NH<sub>4</sub>)<sup>+</sup>.

Example 1109F3(S)-Benzyloxymethyl-4-t-butoxycarbonylmorpholine

7760 A solution of example 1109E (261 mg, 1.2 mmol) and benzyl bromide (0.18 mL, 1.44 mmol) in 1 mL of DMF was cooled in an ice bath and treated with sodium hydride (60%, 72 mg, 1.80 mmol) and the mixture stirred for 15 minutes. The cooling bath was removed and stirring continued for 6 hours and then the mixture was quenched by the addition of water. The mixture was partitioned between water and 3 portions of ethyl

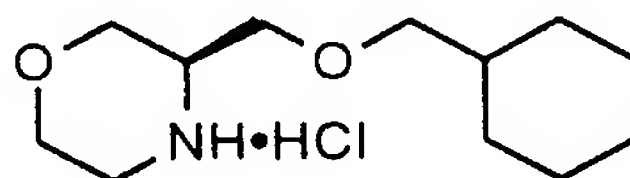
acetate. The combined organic extracts were washed with water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (20 g, 25% ethyl acetate/hexanes) to provide 275 mg (74%) of the title compound. MS (DCI, NH<sub>3</sub>): 308 (MH<sup>+</sup>); 325 (M+NH<sub>4</sub>)<sup>+</sup>.



Example 1109G

3(S)-Cyclohexylmethyloxymethyl-4-t-butoxycarbonylmorpholine

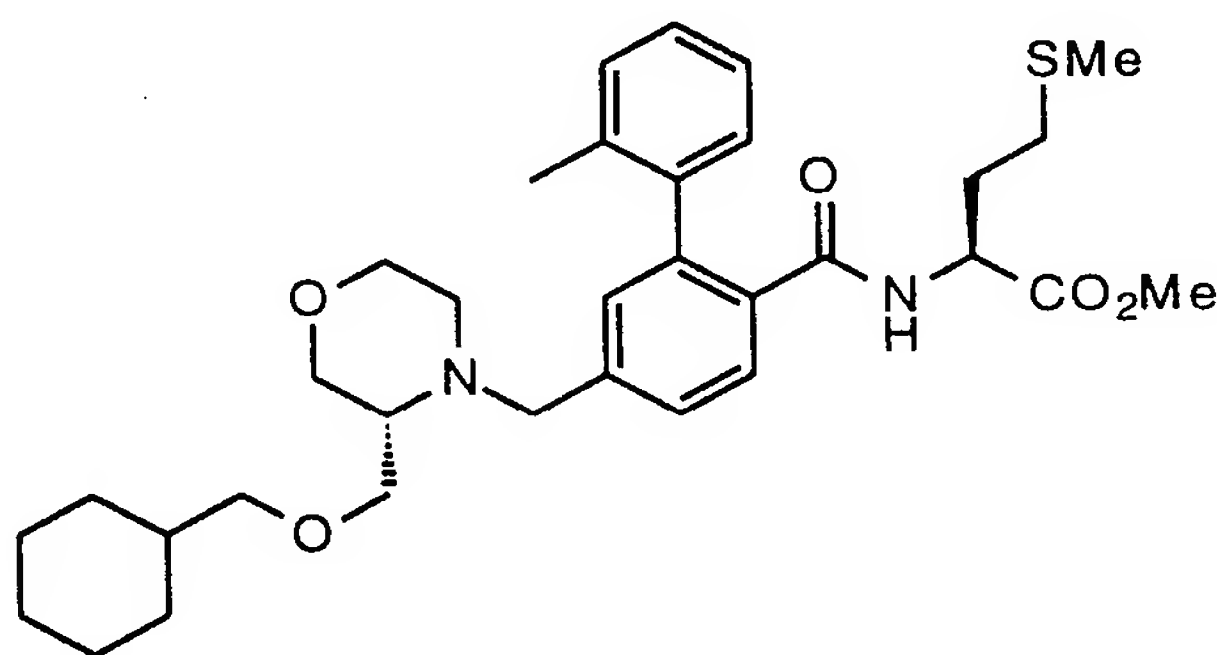
A solution of example 1109F (270 mg, 0.88 mmol) in 15 mL of methanol was treated with 135 mg of 5% rhodium on alumina and stirred under 4 atmospheres of hydrogen gas for 24 hours. The mixture was filtered and concentrated to provide 274 mg (99%) of the title compound. MS (DCI, NH<sub>3</sub>): 314 (MH<sup>+</sup>).



Example 1109H

3(S)-Cyclohexylmethyloxymethylmorpholine

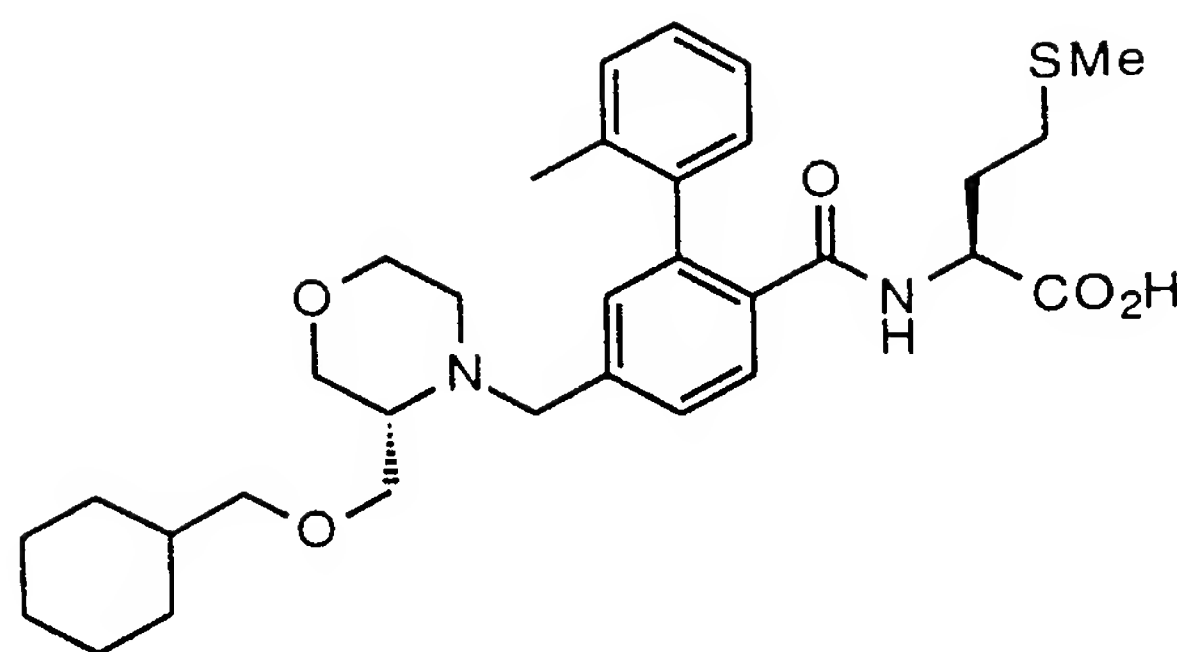
Using the procedure of example 1106C, example 1109G (265 mg, 0.84 mmol) was converted to the title compound. MS (DCI, NH<sub>3</sub>): 214 (MH<sup>+</sup>).



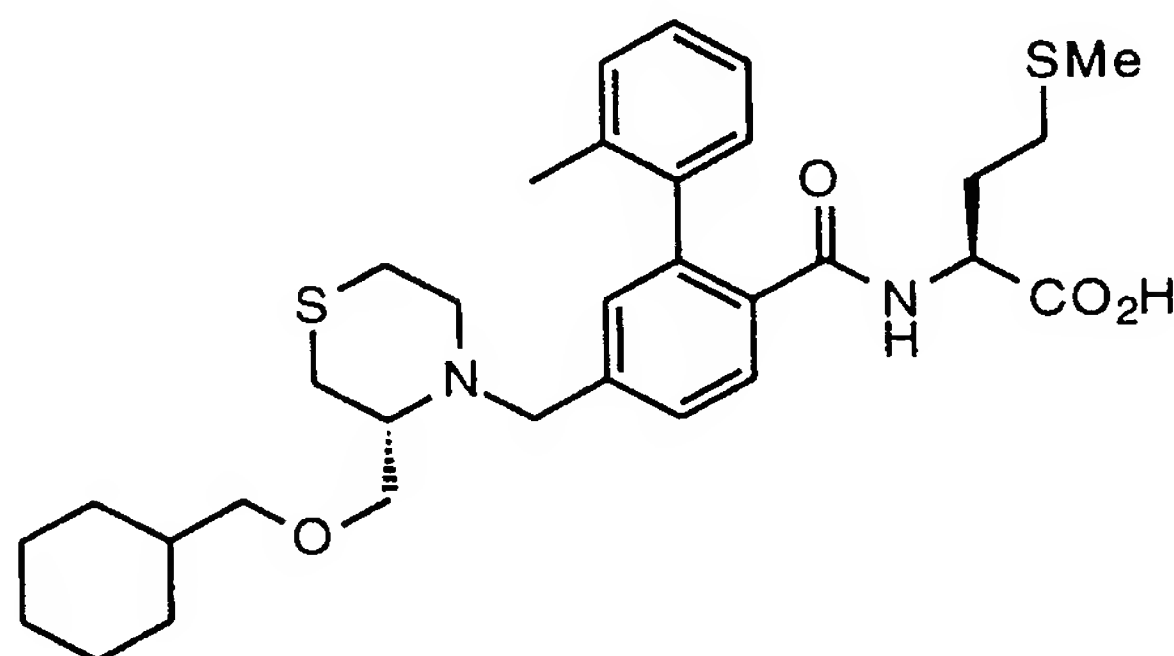
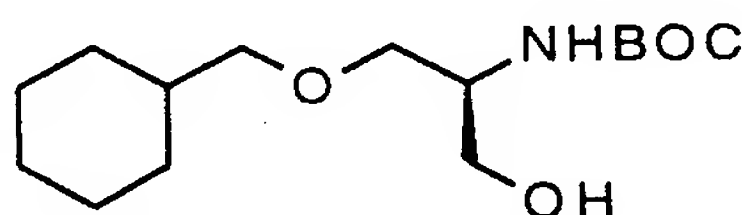
Example 1109I

N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Using the procedure described in example 1106C, part 1, example 1109H (204 mg, 0.82 mmol) provided 29 mg (10%) of the title compound. MS (ESI<sup>+</sup>): 583 (MH<sup>+</sup>); (ESI<sup>-</sup>): 581 (M-H).

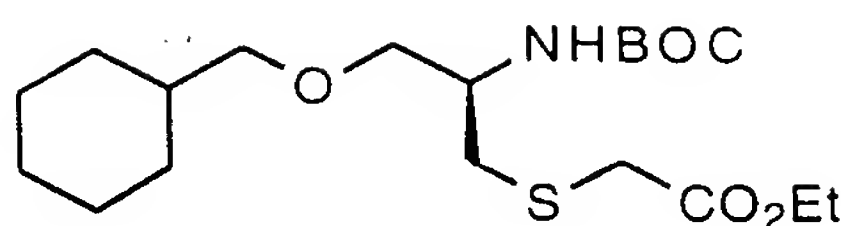
Example 1109JN-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared according to the procedure of example 1104D. <sup>1</sup>H nmr (300 MHz., CD<sub>3</sub>OD): δ 7.64, d, 1H; 7.48, d, 1H; 7.14 - 7.34, m, 5H; 4.41, m, 1H; 4.28, bd, 1H; 3.85, dd, 1H; 3.76, m, 1H; 3.49, 3.70, m, 6H; 3.23, d, 2H; 2.82, m, 2H; 2.51, m, 1H; 2.06 - 2.24, m, 5H; 1.99, s, 3H; 1.93, m, 2H; 1.70, m, 6H; 1.55, m, 1H; 1.09 - 1.32, m, 4H; 0.92, m, 2H. MS (ESI+): 569 (MH<sup>+</sup>); (ESI-): 567 (M-H). Calc'd for C<sub>32</sub>H<sub>44</sub>N<sub>2</sub>O<sub>5</sub>S•0.40 H<sub>2</sub>O; C 66.73; H 7.84; N 4.86; Found: C 66.72; H 7.82; N 4.71.

Example 1111FN-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionineExample 1111A3(S)-cyclohexylmethoxy-2-t-butoxycarbonylaminopropan-1-ol

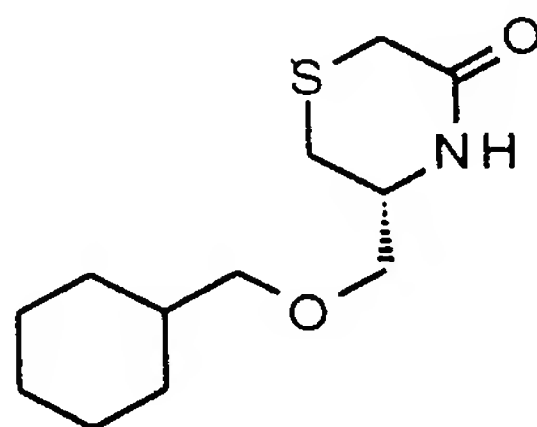
Following the procedure of example 1109G, example 1108A (1.00g, 3.55 mmol) was converted to 0.85 g (83%) of the title compound. MS (DCI, NH<sub>3</sub>): 288 (MH<sup>+</sup>).



Example 1111B

R-[2-t-butoxycarbonylamino-3-cyclohexylmethyloxy]propylmercaptoacetic acid, ethyl ester

7820 Following the procedure described in example 1106B (and substituting the potassium salt of ethyl mercaptoacetate for sodium thiomethoxide), example 1111A (0.84 g, 2.91 mmol) was converted to 0.89 g (78% overall) the title compound. MS (DCI, NH<sub>3</sub>): 390 (MH<sup>+</sup>).



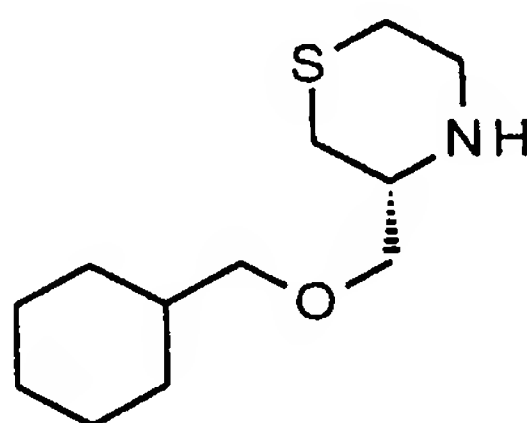
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Example 1111C

3-Oxo-5(R)-cyclohexylmethyloxymethyl-thiomorpholine

7830 Example 1111B (0.88 g, 2.24 mmol) was dissolved in 4 mL of 4N HCl/dioxane and the mixture stirred overnight and concentrated. The residue was dissolved in 5 mL of acetonitrile and diisopropylethylamine (0.80 ml, 4.48 mmol) was added. The mixture was stirred for 1 hour at room temperature and 4 days at 65°C. The mixture was cooled to room temperature, diluted with water and extracted with 3 portions of ethyl ether. The combined organic extracts were washed with 1M aqueous phosphoric acid, water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (30 g, 40% - 100% ethyl acetate/hexanes) to provide 0.35 g (65%) of the title compound. MS (DCI, NH<sub>3</sub>): 244 (MH<sup>+</sup>); 261 (M+NH<sub>4</sub>)<sup>+</sup>.

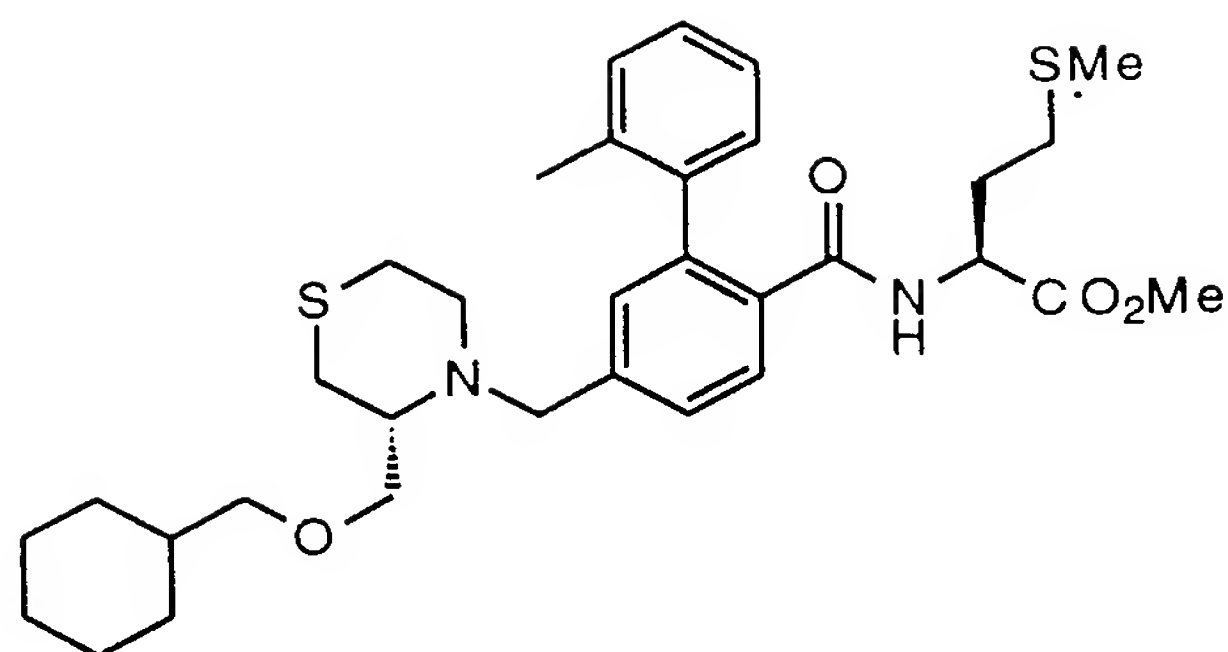
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Example 1111D

5(R)-cyclohexylmethyloxymethyl-thiomorpholine

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Following the procedure of example 1178F, example 1111C (0.34 g, 1.40 mmol) provided 0.34 g (100%) of the title compound. MS (DCI, NH<sub>3</sub>): 230 (MH<sup>+</sup>).



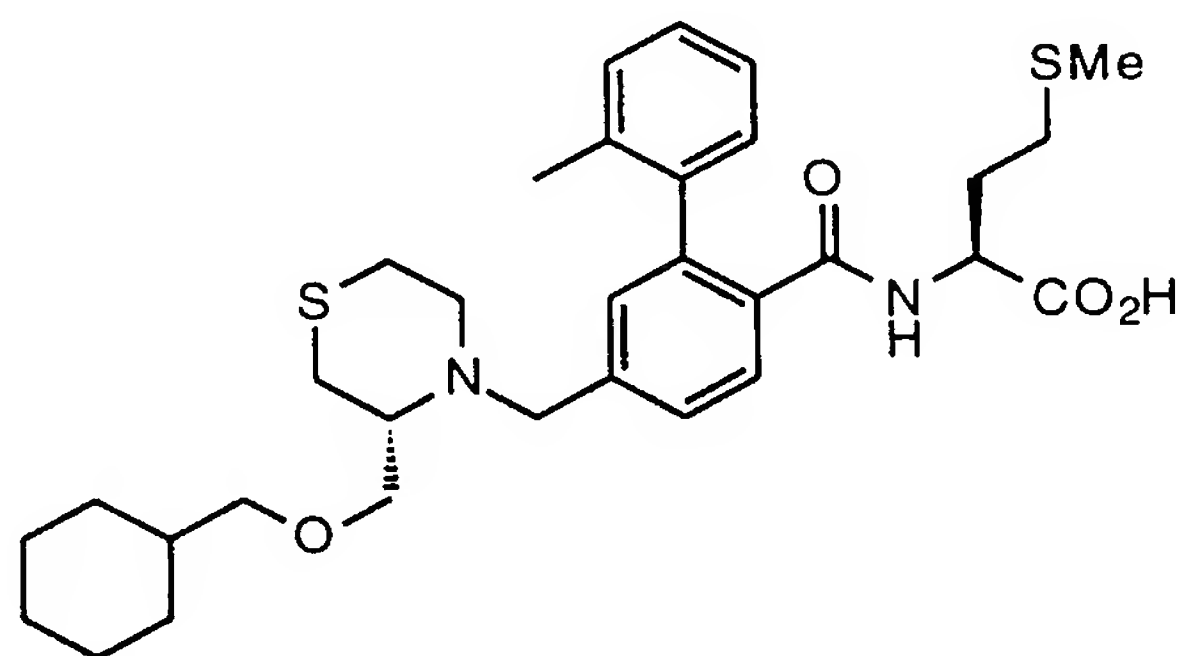
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Example 1111E

N-[4-(3-(R)cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1103C, example 1111D (172 mg, 0.75 mmol) was converted to 67 mg (11%) of the title compound. MS (ESI+): 599 (MH+); (ESI-):

7850 597 (M-H).

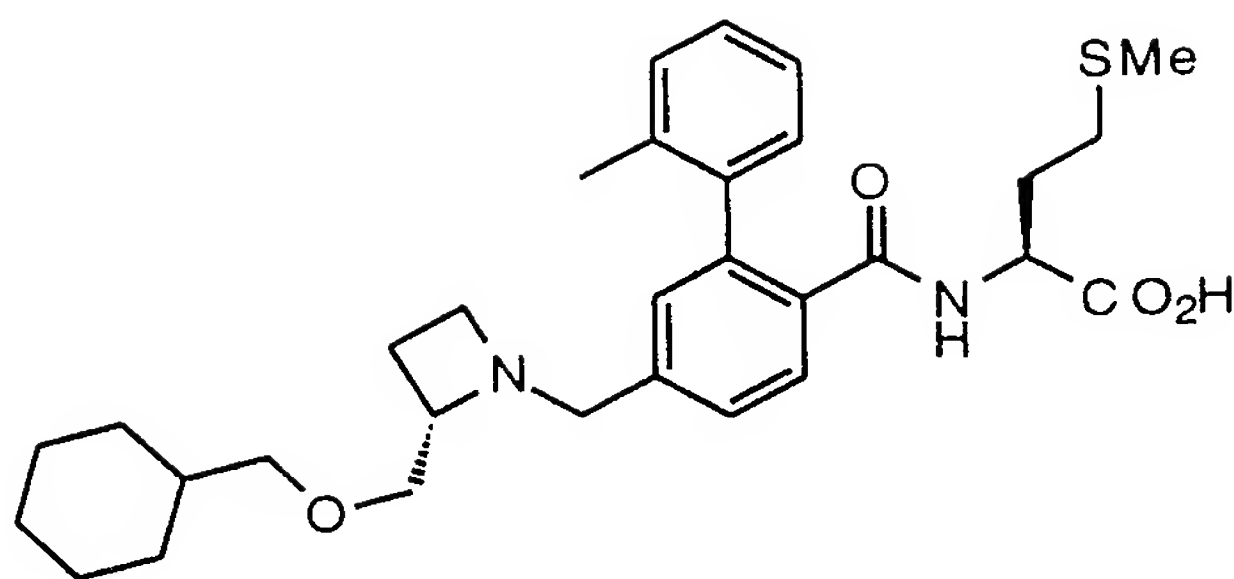
Example 1111F

N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7855

Following the procedure of example 1104D, the title compound was prepared. <sup>1</sup>H nmr (300 MHz., CD<sub>3</sub>OD): δ 7.65, d, 1H; 7.48, d, 1H; 7.14 - 7.32, m, 5H; 4.40, m, 1H; 4.10, d, 1H; 3.91, d, 1H; 3.80, dt, 1H; 3.24, dd, 2H; 3.16, m, 2H; 2.84, m, 2H; 2.56 - 2.77, m, 3H; 2.05 - 2.13, m, 5H; 2.00, s, 3H; 1.93, m, 2H; 1.69, m, 6H; 1.55, m, 1H; 1.09 - 1.32, m, 4H; 0.94, m, 2H. MS (ESI+): 585 (MH+); (ESI-): 583 (M-H). Calc'd for C<sub>32</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>•0.30 H<sub>2</sub>O; C 65.12; H 7.62; N 4.75; Found: C 65.14; H 7.72; N 4.60.

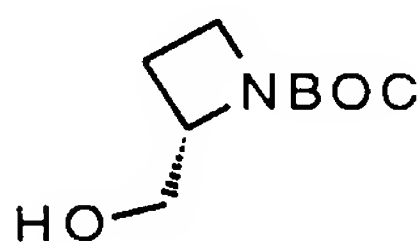
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Example 1114

N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine



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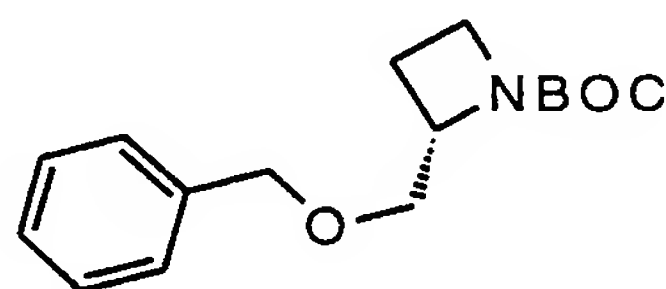
Example 1114A

N-t-Butoxycarbonyl-2(S)-hydroxymethylazetidine

Azetidine-2-carboxylic acid (1.25 g, 12.4 mmol) was dissolved in 10 mL of 2M aqueous sodium carbonate and a solution of di-tert-butyldicarbonate in 10 mL of THF was added and the mixture was stirred overnight. The mixture was diluted with water and ether and the layers were separated. The ether layer was washed with water and pH of the combined aqueous phases adjusted to ~ 2 with phosphoric acid. The mixture was extracted with 4 portions of 20% isopropanol/chloroform and the combined organic phases were dried, filtered and concentrated. The residue was dissolved in 15 mL of THF and cooled in an ice bath. The solution was treated with 25 mL of borane in THF (1M, 25 mmol) and stirring was continued for 1 hour. The ice bath was removed and the solution stirred for 2 hours and then quenched by the careful addition of 25 mL of 4:1 THF/water. The mixture was stirred for 15 minutes, carefully treated with 25 mL of 1N aqueous HCl, and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with 2 additional portions of ethyl acetate. The combined organic fractions were washed with 2M aqueous sodium carbonate, water, brine, and dried, filtered and concentrated to provide 2.18 g (94%) of the title compound. MS (DCI, NH<sub>3</sub>): 188 (MH<sup>+</sup>).

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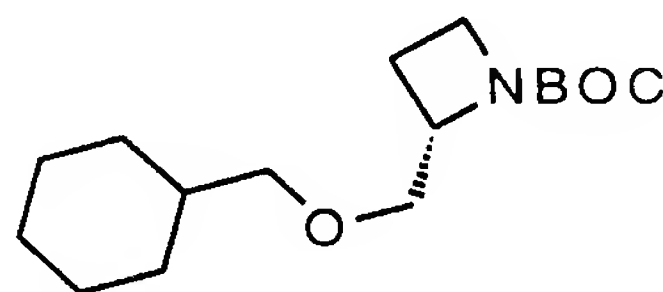


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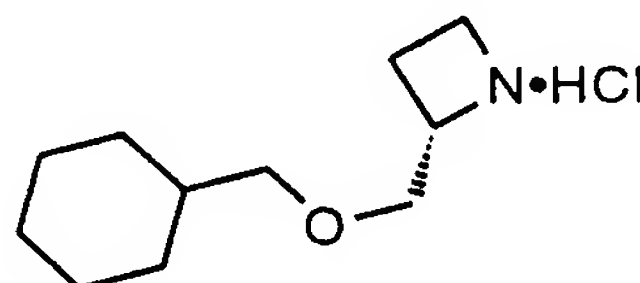
Example 1114B

N-t-Butoxycarbonyl-2(S)-benzyloxymethylazetidine

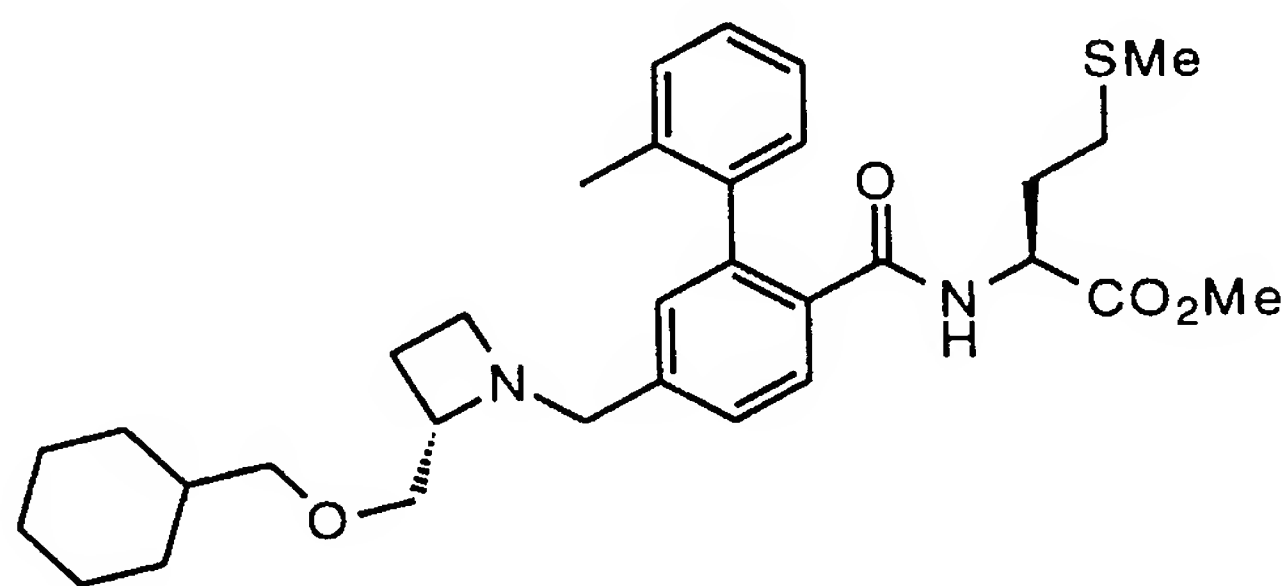
Following the procedure of example 1109F, example 1114A (0.94 g, 5 mmol) was converted to the crude product. The crude residue was purified by chromatography on silica gel (50 g, 20% ethyl acetate/hexanes) to provide 0.44 g, (32%) of the title compound. MS (DCI, NH<sub>3</sub>): 278 (MH<sup>+</sup>).

Example 1114CN-t-Butoxycarbonyl-2(S)-cyclohexylmethyloxymethylazetidine

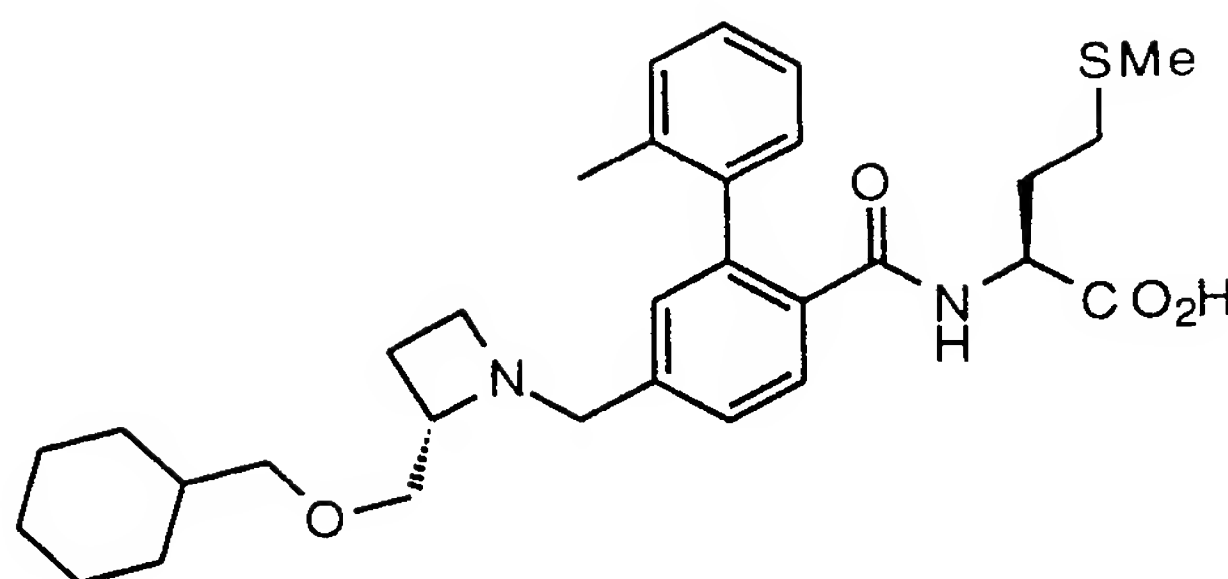
Following the procedure described in example 1109G, example 1114B (0.43 g, 1.56 mmol) provided 0.42 g, (95%) of the title compound. MS (DCI, NH<sub>3</sub>): 284 (MH<sup>+</sup>).

Example 1114D2(S)-cyclohexylmethyloxymethylazetidine, hydrochloride salt

Following the procedure described in example 1106C, example 1114C (0.42 g, 1.48 mmol) was converted to 0.32 g (100%) of the title compound. MS (DCI, NH<sub>3</sub>): 184 (MH<sup>+</sup>).

Example 1114EN-[4-(2(S)-cyclohexylmethyloxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure described in example 1106D, part 1, example 1114D (220 mg, 1.0 mmol) provided 145 mg (53%) of the title compound. MS (ESI<sup>+</sup>): 553 (MH<sup>+</sup>); (ESI<sup>-</sup>): 551 (M-H).

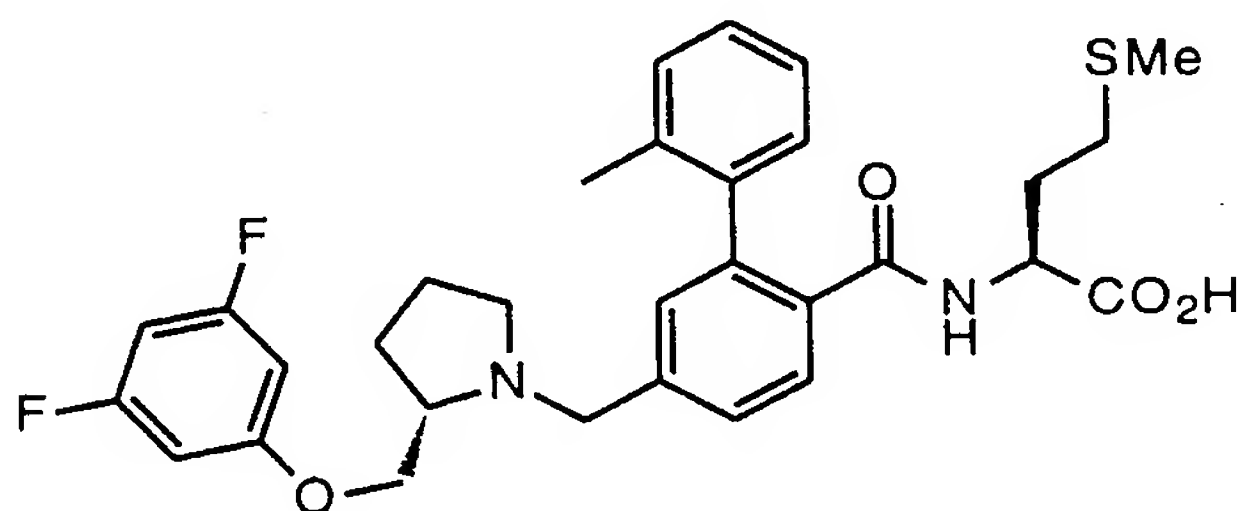
Example 1114F

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N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 114E (100 mg, 0.18 mmol) provided 92 mg (95%) of the title compound. <sup>1</sup>H nmr (300 MHz., dmso d<sub>6</sub>): δ 8.10, bd, 1H; 7.47, d, 1H; 7.33, d, 1H; 7.20, m, 2H; 7.11, m, 3H; 4.21, m, 1H; 3.83, d, 1H; 3.54, d, 1H; envelope 3.07 - 3.48, m, 4H; 2.84, m, 1H; 1.98 - 2.22, m, 5H; 1.97, s, 3H; envelope, 0.77 - 1.95, 17H. MS (ESI<sup>+</sup>): 539 (MH<sup>+</sup>); (ESI<sup>-</sup>): 537 (M-H). Calc'd for C<sub>31</sub>H<sub>42</sub>N<sub>2</sub>O<sub>4</sub>S•0.90 H<sub>2</sub>O; C 67.09; H 7.96; N 5.05; Found: C 67.09; H 7.84; N 5.00.

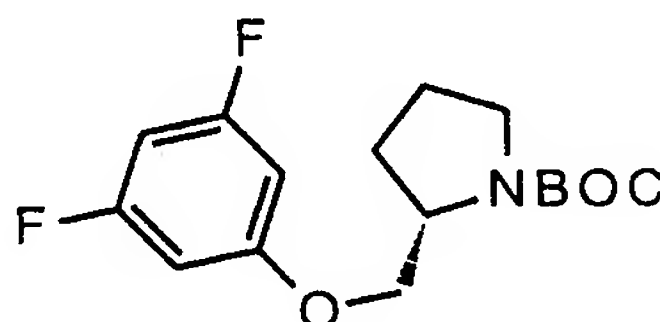
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Example 1115

N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine



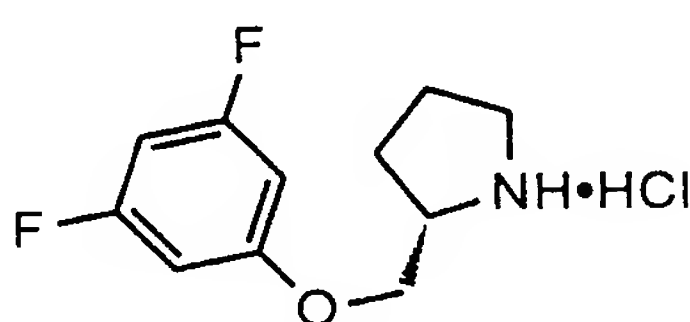
7935

Example 1115A

N-t-Butoxycarbonyl-2(S)-(3,5-difluorophenoxy)pyrrolidine

A solution of N-t-butoxycarbonyl-2-hydroxymethylpyrrolidine (0.40 g, 2.00 mmol), triphenylphosphine (1.05 g, 4.00 mmol), and 3,5-difluorophenol (0.52 g, 4.00

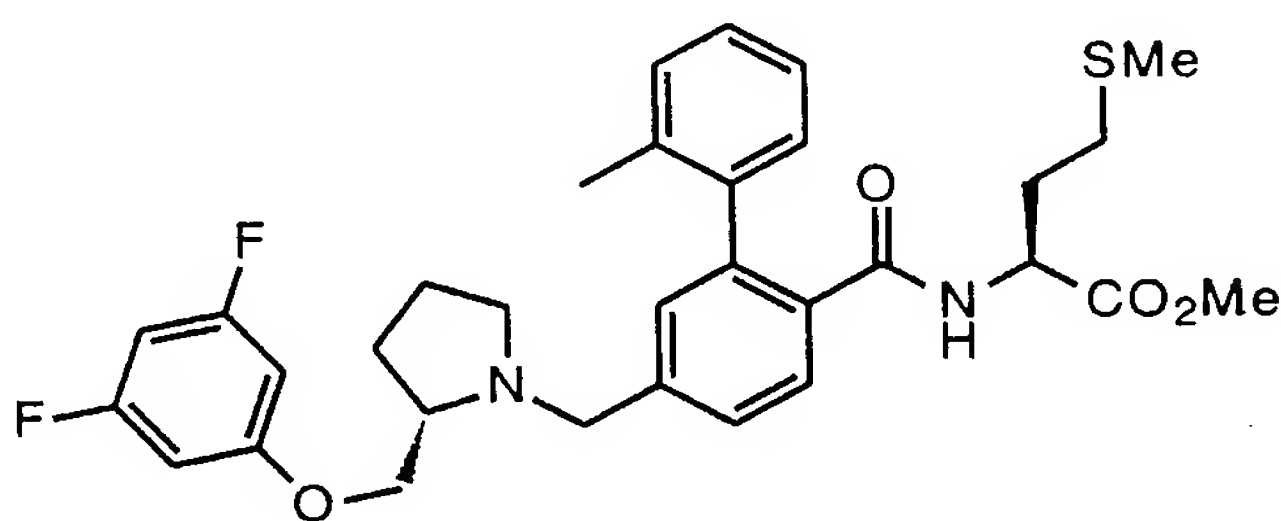
7940 mmol) in 5 mL of 1,2-dichloroethane was cooled in an ice bath and treated with a solution of diethylazodicarboxylate (0.63 mL, 4.00 mmol) in 3 mL of toluene. The cooling bath was removed and the solution was stirred for 70 hours at ambient temperature. The mixture was diluted with ether and extracted with 4N aqueous sodium hydroxide, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (30 g, 10% ethyl acetate/hexanes) provided 0.49 g, (80%) of the title compound. MS (DCI, NH<sub>3</sub>): 314 (MH<sup>+</sup>).



Example 1115B

7950 2(S)-(3,5-difluorophenoxy)pyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1115A (0.48 g, 1.53 mmol) was provided 0.35 g (91%) of the title compound. MS (DCI, NH<sub>3</sub>): 214 (MH<sup>+</sup>); 231 (M+NH<sub>4</sub>)<sup>+</sup>.

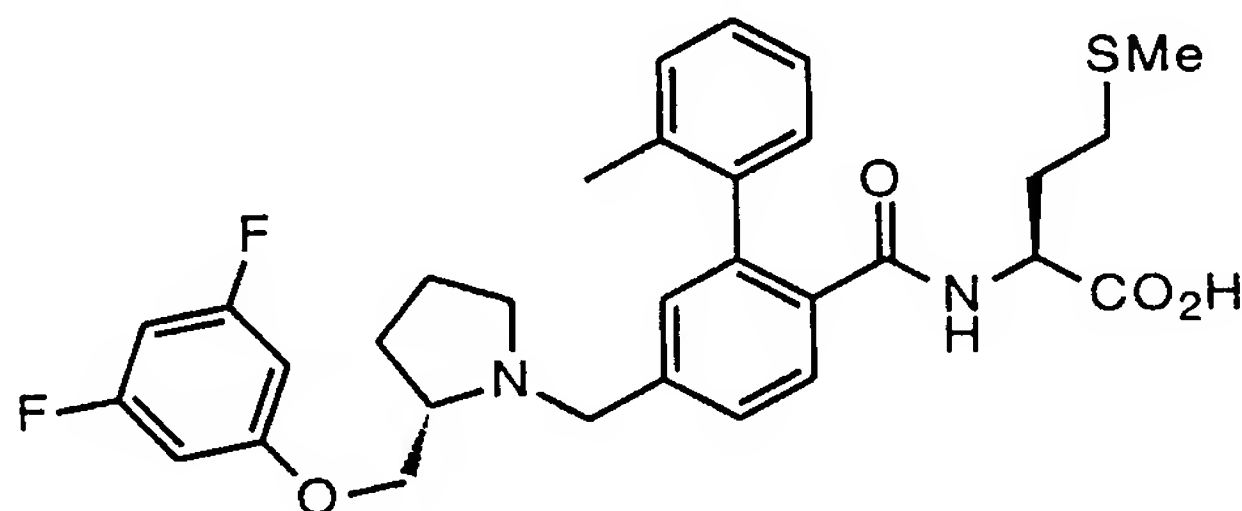


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Example 1115C

N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

7960 Following the procedure of example 1106C, part 1, example 1115B (0.19 g, 0.75 mmol) provided 0.22 g (76%) of the title compound. MS (ESI<sup>+</sup>): 583 (MH<sup>+</sup>); (ESI<sup>-</sup>): 581 (M-H).



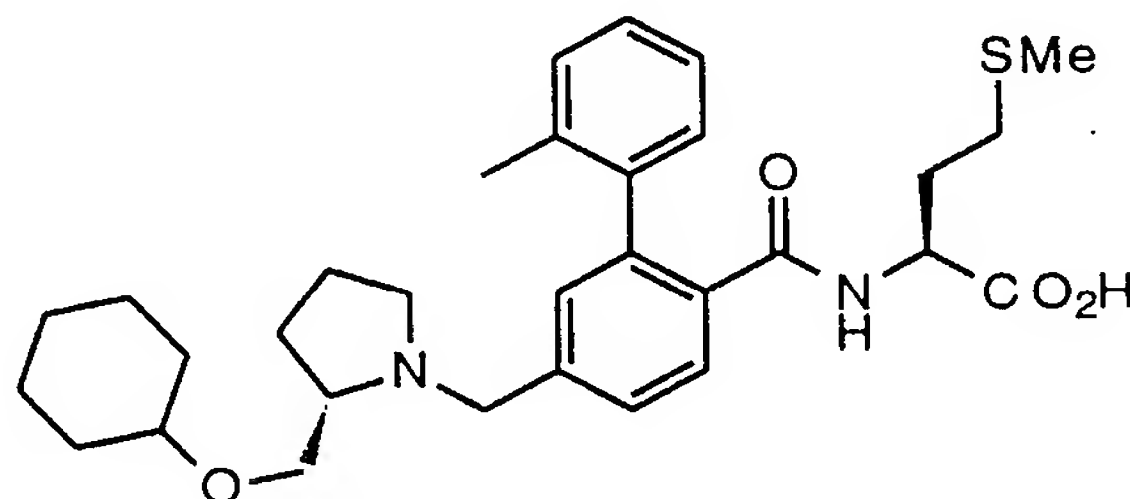
Example 1115D

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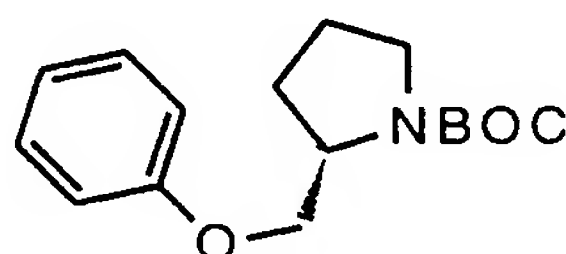
N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

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Following the procedure of example 1104D, example 1115C (0.21 g, 0.36 mmol) provided the title compound.  $^1\text{H}$  nmr (300 MHz.,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.69, d, 1H; 7.53, dd, 1H; 7.33, m, 1H; 7.05 - 7.29, m, 4H; 6.48 - 6.62, m, 3H; 4.48, m, 1H; 4.34, m, 1H; 4.12, m, 3H; 3.65, m, 1H; 3.31, m, 1H; 2.96, m, 1H; envelope 1.82 - 2.41, 13H; 1.68, m, 1H. MS (ESI+): 569 (MH+); (ESI-): 567 (M-H). Calc'd for  $\text{C}_{31}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_4\text{S} \cdot 0.35 \text{H}_2\text{O}$ ; C 64.76; H 6.08; N 4.87; Found: C 64.72; H 5.97; N 4.75.



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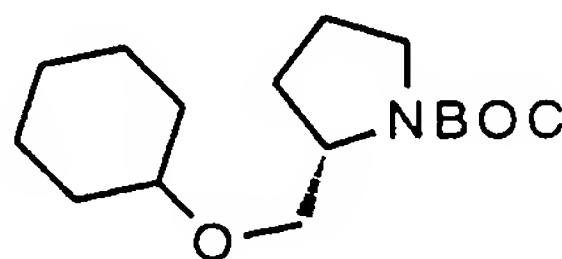
Example 1116N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

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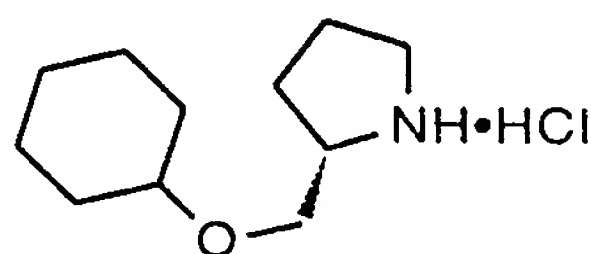
Example 1116AN-t-Butoxycarbonyl-2(S)-phenoxyethylpyrrolidine

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Following the procedure of example 1115 A, N-t-butoxycarbonyl-2-hydroxyethylpyrrolidine (0.80 g, 4.00 mmol) and phenol (1.13 g, 12.00 mmol) provided 0.99 g (89%) of the title compound. MS (DCI,  $\text{NH}_3$ ): 278 (MH+).

Example 1116BN-t-Butoxycarbonyl-2(S)-cyclohexyloxymethylpyrrolidine

7990 Following the procedure of example 1109G, example 1116A (0.56 g, 2.00 mmol) provided 0.55 g (96%) of the title compound. MS (DCI, NH<sub>3</sub>): 284 (MH<sup>+</sup>).

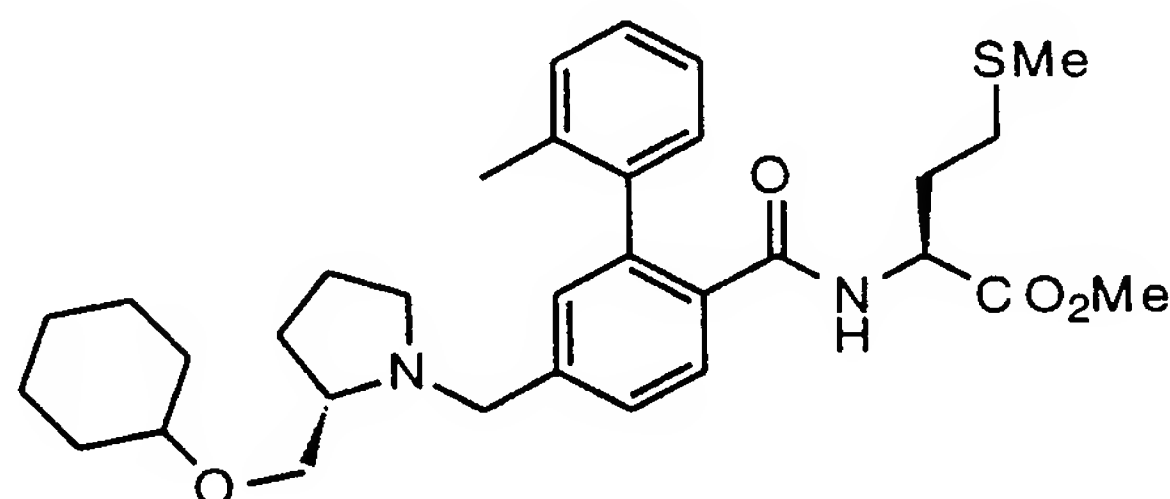


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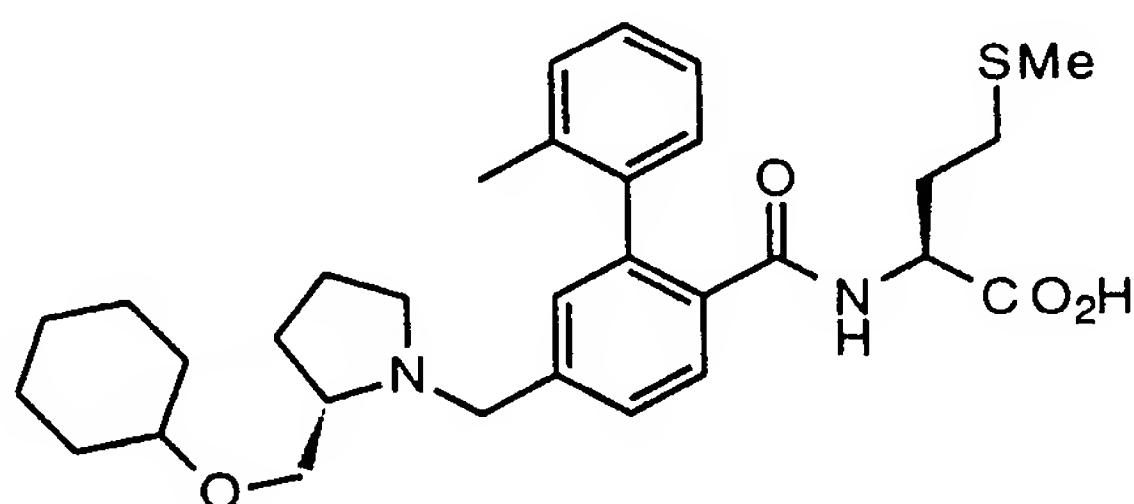
Example 1116C2(S)-cyclohexyloxymethylpyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1116B (0.54 g, 1.90 mmol) provided 0.41g (99%) of the title compound. MS (DCI, NH<sub>3</sub>): 184 (MH<sup>+</sup>); 201 (M+NH<sub>4</sub>)<sup>+</sup>.

8000

Example 1116DN-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8005 Following the procedure of example 1106D, part 1, example 1116C (0.22 g, 1.00 mmol) provided 0.22 g (83%) of the title compound. MS (ESI<sup>+</sup>): 553 (MH<sup>+</sup>); (ESI<sup>-</sup>): 551 (M-H).



8010

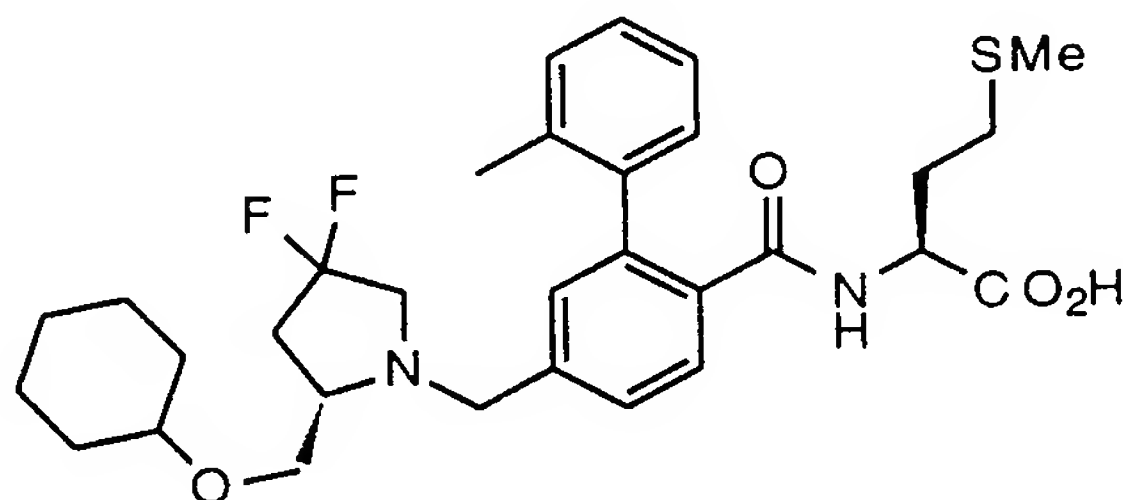
Example 1116EN-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1116D (0.22 g, 0.40 mmol) provided 0.18 g (81%). <sup>1</sup>H nmr (300 MHz., dmso d<sub>6</sub>): δ 8.09, bd, 1H; 7.48, d, 1H; 7.36,



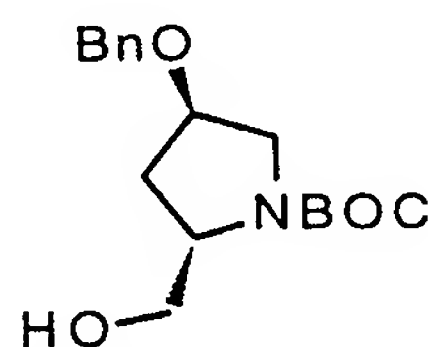
8015 d, 1H; 7.21, m, 2H; 7.13, m, 3H; 4.21, m, 2H; 3.49, d, 1H; envelope 3.15 - 3.45, 3H; 2.84, m, 1H; 2.70, m, 1H; 2.00 - 2.29, m, 7H; 1.96, s, 3H; 1.34 - 1.94, m, 8H; 1.18, m, 6H. MS (ESI+): 539 (MH+); (ESI-): 537 (M-H). Calc'd for C<sub>31</sub>H<sub>42</sub>N<sub>2</sub>O<sub>4</sub>S•0.50 H<sub>2</sub>O; C 67.98; H 7.91; N 5.11; Found: C 67.95; H 7.81; N 5.05.

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Example 1117

N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

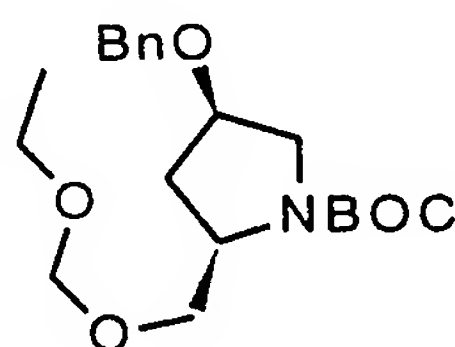
8025

Example 1117A

N-t-butoxycarbonyl-2(S)-hydroxymethyl-4(R)-benzyloxypyrrolidine

8030 A solution of trans-N-t-butoxycarbonyl-4-benzyloxy-L-proline (3.32 g, 10.3 mmol) in 20 mL of THF was cooled in an ice/acetone bath and a solution of borane in THF (1M, 20.6 mL, 20.6 mmol) was added dropwise. The solution was stirred for 2 hours then the cooling bath was removed and the mixture stirred overnight. The reaction was quenched by the careful addition of water followed by the addition of 20 mL of 1N aqueous HCl and then poured into ethyl acetate. The layers were separated and the aqueous layer extracted with 2

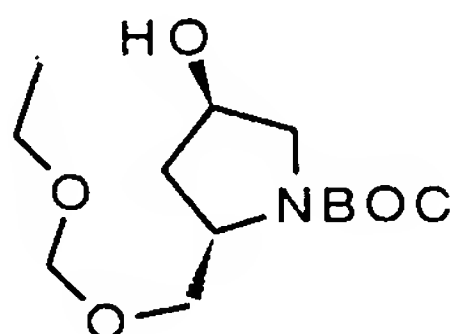
8035 portions of ethyl acetate. The combined organic extracts were 2M aqueous sodium carbonate, water and brine, dried, filtered and concentrated to provide 3.19 g (100%) of the title compound. MS (DCI, NH<sub>3</sub>): 308 (MH<sup>+</sup>).



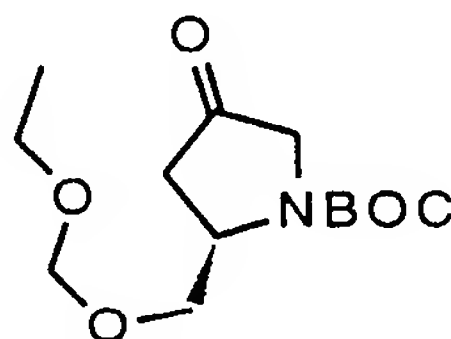
8040

Example 1117BN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-benzyloxypyrrolidine

A solution of example 1117A (2.14 g, 7.00 mmol) in 15 mL of methylene chloride was cooled in an ice bath and treated with diisopropylethylamine (1.87 mL, 10.50 mmol) followed by the addition of chloromethylethyl ether (0.97 mL, 10.50 mmol). The cooling bath was removed, the mixture stirred for 24 hours and then poured into 100 mL of ethyl ether. The organic phase washed with water, aqueous HCl, brine, dried, filtered and concentrated to provide 2.32 g (94%) of the title compound. MS (DCI, NH<sub>3</sub>): 366 (M + NH<sub>4</sub>)<sup>+</sup>.

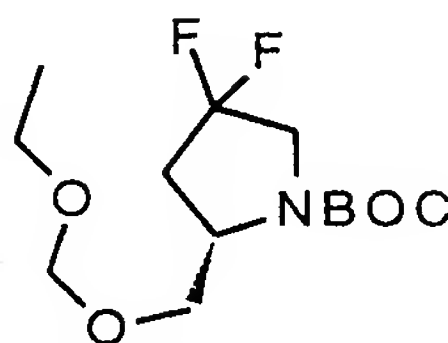
Example 1117CN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-hydroxypyrrolidine

A solution of example 1117B (2.29 g, 6.50 mmol) in 20 mL of degassed methanol was treated with Perleman's catalyst (0.40 g) and then the mixture was stirred under a balloon of hydrogen gas overnight. The mixture was diluted with ethyl acetate and filtered through a plug of silica gel. The silica gel plug was washed well with ethyl acetate and the filtrate concentrated to provide 1.77 g (99%) of the title compound. MS (DCI, NH<sub>3</sub>): 276 (MH<sup>+</sup>).

Example 1117DN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4-oxopyrrolidine

A solution of example 1117C (0.99 g, 3.59 mmol) in 20 mL of 10% acetonitrile/methylene chloride was treated with powdered, activated 4Å molecular sieves (1 g), 4-methylmorpholine-4-oxide (0.63 g, 5.38 mmol) and the mixture stirred for 30 minutes. The suspension was treated with tetrapropylammonium perruthenate (0.04g, 0.11 mmol) and the resulting black mixture stirred for 30 minutes. The mixture was treated with ~ 3 g of celite and diluted with 30 mL of ether and stirred for 20 minutes. The suspension was then filtered through a pad of silica gel (which was washed well with ether) and the

filtrate concentrated to provide 0.91 g (93%) of the title compound. MS (DCI, NH<sub>3</sub>): 274 (MH<sup>+</sup>); 291 (M+NH<sub>4</sub>)<sup>+</sup>.

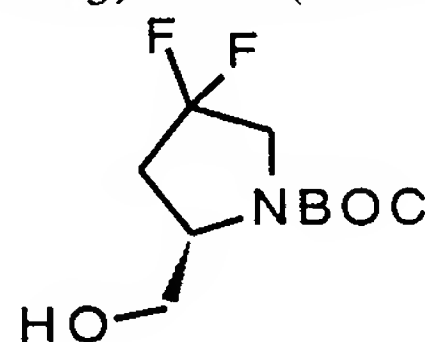


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Example 1117EN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4,4--difluoropyrrolidine

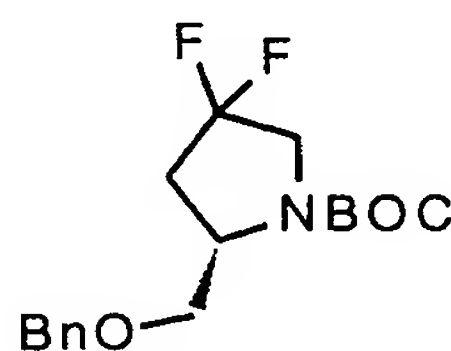
A solution of example 1117D (0.90 g, 3.30 mmol) in 20 mL of methylene chloride was cooled in an dry ice/acetone bath and treated with DAST (1.80 mL, 13.20 mmol). The bath was removed and the mixture stirred for 48 hours, cooled in an ice bath and carefully quenched by the addition of 2M aqueous sodium carbonate. The layers were separated and the aqueous layer was extracted with 2 additional portions of methylene chloride and the combined organic fractions were dried, filtered and concentrate. The residue was purified by column chromatography on silica gel (40 g, 15% ethyl acetate/hexanes) provided 0.70 g (72%) of the title compound. MS (DCI, NH<sub>3</sub>): 296 (MH<sup>+</sup>); 313 (M+NH<sub>4</sub>)<sup>+</sup>.

8085

Example 1117FN-t-butoxycarbonyl-2(S)-hydroxymethyl-4,4--difluoropyrrolidine

A solution of example 1117E (0.69 g, 2.30 mmol) in 10 mL of methanol was treated with 0.5 mL of concentrated aqueous HCl and the mixture stirred overnight. The yellow solution was poured into 2M aqueous sodium carbonate and concentrated to remove the methanol. The mixture was diluted with THF and ~1 g of di-t-butyldicarbonate was added and the mixture stirred for 3 hours and diluted with ethyl ether. The phases were separated and the aqueous phase was extracted with 3 portions of methylene chloride. The combined organic phases were dried, filtered and concentrated to provide 0.48 g (88%) of the title compound. MS (DCI, NH<sub>3</sub>): 238 (MH<sup>+</sup>); 255 (M+NH<sub>4</sub>)<sup>+</sup>.

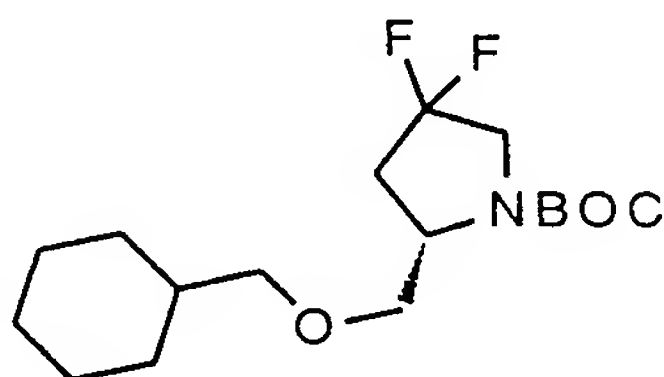
8095

Example 1117G

N-t-butoxycarbonyl-2(S)-benzyloxymethyl-4,4--difluoropyrrolidine

8100

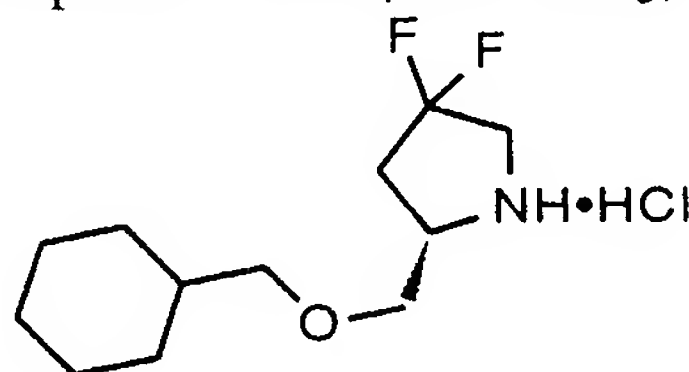
Following the procedure of example 1109F, example 1117G (0.24 g, 1.00 mmol) provided 0.26 g (78%) of the title compound. MS (DCI, NH<sub>3</sub>): 328 (MH<sup>+</sup>).

Example 1117H

8105

N-t-butoxycarbonyl-2(S)-cyclohexylmethyloxymethyl-4,4--difluoropyrrolidine

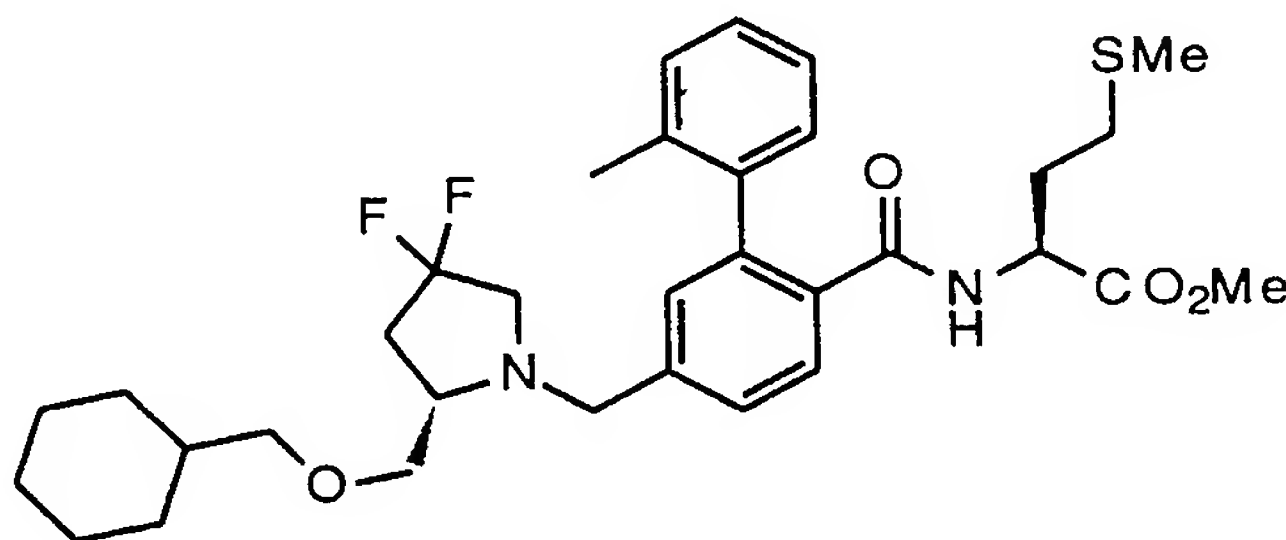
Following the procedure of example 1109G, example 1117G (0.25 g, 1.10 mmol) provided 0.22 g (87%) of the title compound. MS (DCI, NH<sub>3</sub>): 334 (MH<sup>+</sup>).

Example 1117I

8110

2(S)-cyclohexylmethyloxymethyl-4,4--difluoropyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1117H (0.22 g, 0.92 mmol) provided 0.17 g (98%) of the title compound. MS (DCI, NH<sub>3</sub>): 234 (MH<sup>+</sup>).

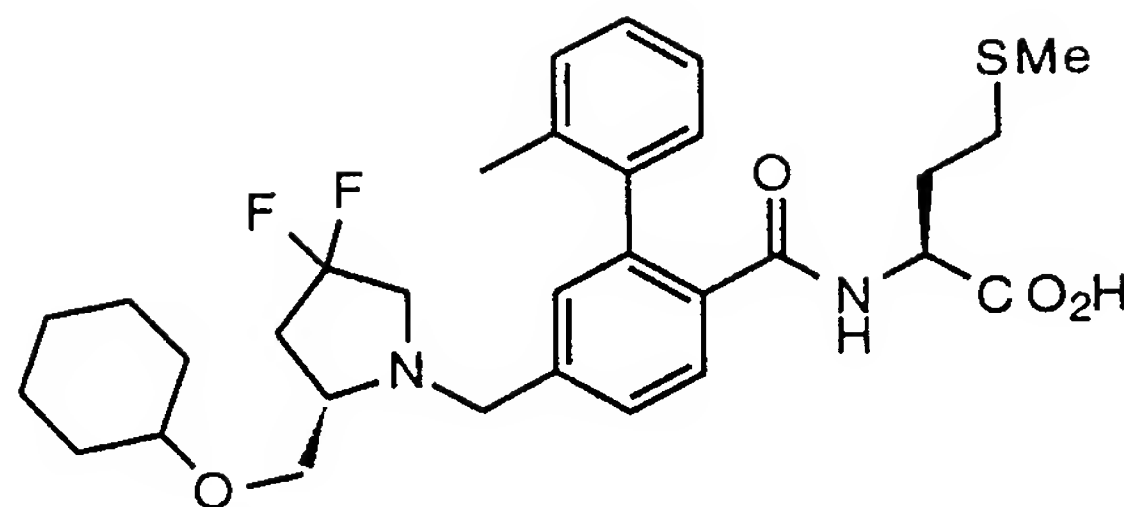


8115

Example 1117JN-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1106D, part 1, example 1117I (0.16 g, 0.60 mmol) provided 0.13 g (43%) of the title compound. MS (ESI<sup>+</sup>): 603 (MH<sup>+</sup>): (ESI<sup>-</sup>): 601 (M-H).

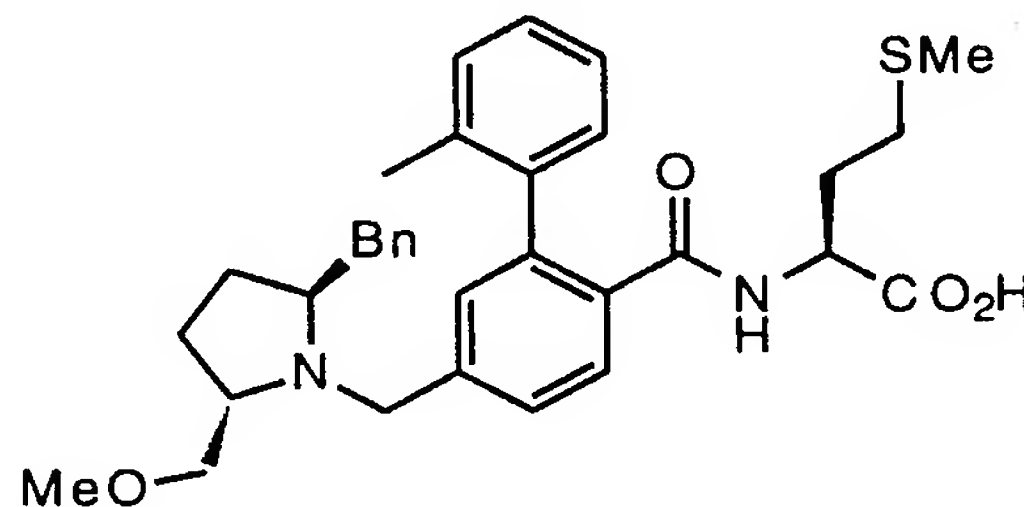
8120



Example 1117K

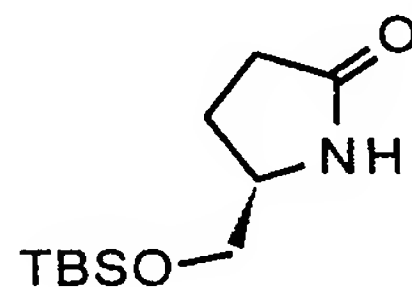
N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1117J (123 mg, 0.20 mmol) provided 116 mg (98%) of the title compound. <sup>1</sup>H nmr (300 MHz., CD<sub>3</sub>OD): δ 7.62, d, 1H; 7.43, d, 1H; 7.13 - 7.32, m, 5H; 4.44, m, 1H; 4.26, d, 1H; 3.56, d, 1H; 3.54, dd, 1H; 3.48, dd, 1H; 3.24, m, 2H; 3.10, m, 1H; 2.71, m, 1H; 2.37, m, 1H; 2.03 - 2.25, m, 6H; 2.00, s, 3H; 1.87 - 2.00, m, 1H; 1.68, m, 5H; 1.53, m, 1H; 1.18, m, 3H; 0.90, m, 2H. MS (ESI+): 589 (MH<sup>+</sup>); (ESI-): 587 (M-H). Calc'd for C<sub>32</sub>H<sub>42</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S; C 65.28; H 7.19; N 4.76; Found: C 64.99; H 7.16; N 4.54.



Example 1118

N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

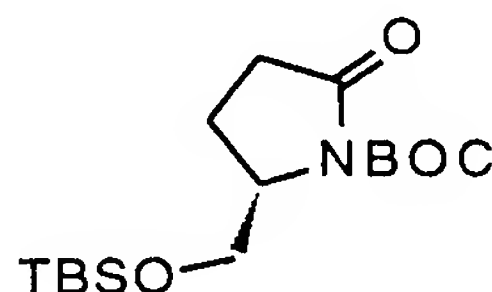


Example 1118A

5(S)-t-butyldimethylsiloxymethyl-2-pyrrolidinone

A stirred solution of 5(S)-hydroxymethyl-2-pyrrolidinone (5.00 g, 0.043 mol) in 20 mL of DMF was treated with imidazole (6.81 g, .10 mol) and then t-butyldimethylchlorosilane (7.20 g, 0.047 mol) and the mixture stirred for 2 hours. The thick

mixture was diluted with water and extracted with 3 portions of ethyl acetate. The combined ethyl acetate layer were washed with water, brine, dried filtered and concentrated to provide 7.50 g (75%) of the title compound. MS (DCI, NH<sub>3</sub>): 230 (MH<sup>+</sup>); 247 (M+NH<sub>4</sub>)<sup>+</sup>.



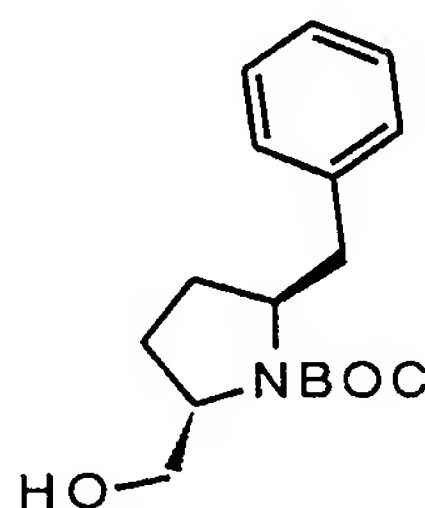
8150

### Example 1118B

#### N-t-butoxycarbonyl-5(S)-t-butyltrimethylsilyloxymethyl-2-pyrrolidinone

A stirred solution of example 1118A (1.65 g, 7.20 mmol) in 5 mL of acetonitrile at rt was treated with DMAP (0.15 g, 1.25 mmol) and di-tert-butyl dicarbonate (1.09 g, 7.20 mmol) and the mixture stirred at ambient temperature for 48 hours at which time an additional 0.80 g of di-tert-butyl dicarbonate was added. The mixture was stirred an additional 6 hours and then diluted with 80 mL of ether and washed with 1M aqueous phosphoric acid, water, brine, dried filtered and concentrated. The residue was purified by column chromatography on silica gel (100 g, 15% ethyl acetate/hexanes) to provide 1.50 g (63%) of the title compound. MS (DCI, NH<sub>3</sub>): 347 (M+NH<sub>4</sub>)<sup>+</sup>.

8160



### Example 1118C

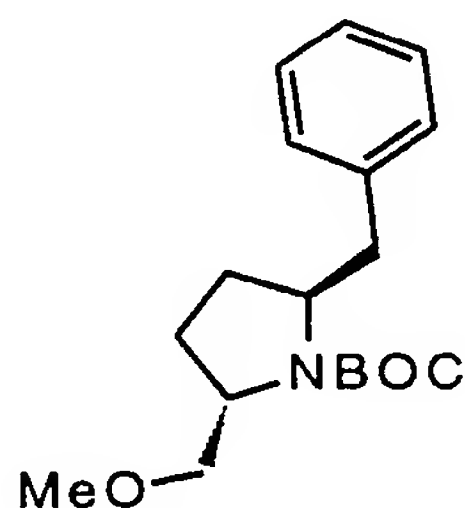
#### N-t-butoxycarbonyl-2(S)-hydroxymethyl-5(S)-benzylpyrrolidine

A solution of example 1118C (1.05 g, 3.17 mmol) in 10 mL of toluene was cooled in a dry ice/acetone bath and treated with diisobutylaluminum hydride (3.2 mL of a 1.5M solution in toluene, 4.75 mmol) and the mixture stirred for 1 hour. The dry ice bath was replaced with an ice/acetone bath and the mixture stirred for an additional hour and then quenched with the careful addition of methanol (0.25 mL) and stirring continued until the evolution of gas ceased. The solution was then treated with 1N aqueous HCl and ethyl acetate and the mixture stirred until 2 clear phases resulted. The aqueous layer was extracted with ethyl acetate and the combined organic fractions were washed with 1N HCl, saturated sodium bicarbonate, brine, dried, filtered and concentrated. The residue was dissolved in 10 mL of methylene chloride and cooled in a dry ice/acetone bath and then treated with boron

8170



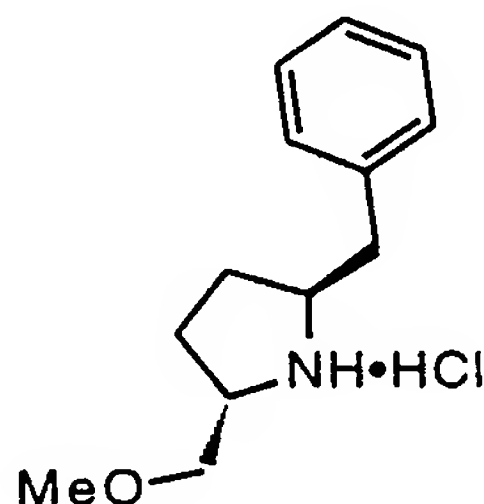
8175 trifluoride etherate (0.41 mL, 3.34 mmol) followed by benzylmagnesium chloride (4 mL of a  
2.0M solution in THF, 8.00 mmol) and the mixture stirred for 1.5 hours and quenched by  
the addition of saturated sodium bicarbonate. The cooling bath was removed and the mixture  
allowed to reach room temperature. The mixture was diluted with ether and extracted with  
8180 ether and the combined organic extracts dried, filtered and concentrated. The residue was  
diluted with THF (10 mL) and treated with TBAF (10 mL of a 1.0M THF solution, 10.0  
mmol) and the mixture stirred overnight. The mixture was diluted with water and extracted  
with 3 portions of ethyl acetate. The combined organic fractions were washed with water,  
brine, dried, filtered and concentrated. The residue was purified by column chromatography  
8185 on silica gel (50 g, 30% ethyl acetate/hexanes) to provide 0.15 g (16%) of the title  
compound. MS (DCI, NH<sub>3</sub>): 292 (MH)<sup>+</sup>.



Example 1118D

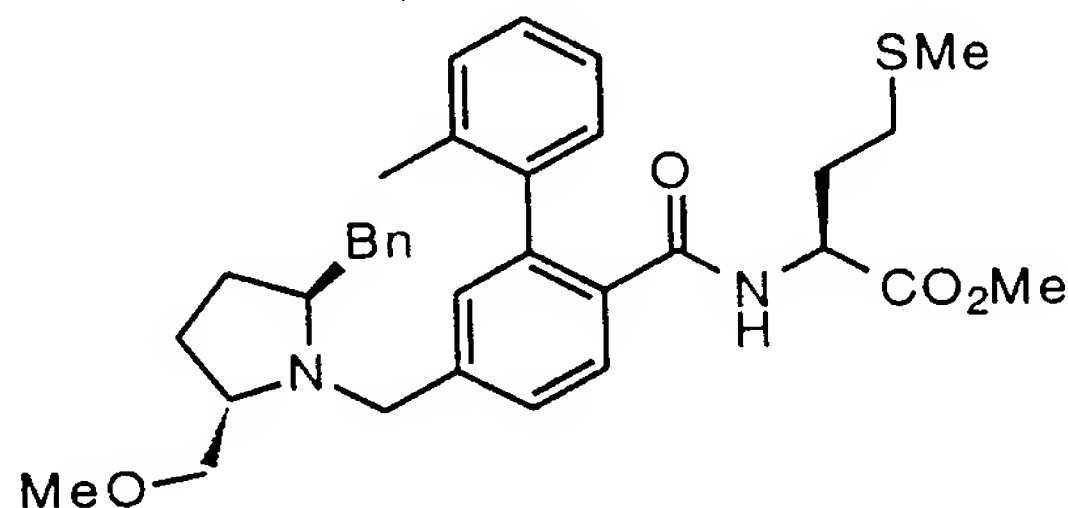
8190 N-t-butoxycarbonyl-2(S)-methoxymethyl-5-benzylpyrrolidine

A solution of example 1118C (224 mg, 0.77 mmol) in 1 mL of DMF was treated with  
methyl iodide (96  $\mu$ L, 1.54 mmol) and cooled in an ice bath. The mixture was treated with  
sodium hydride (60%, 62 mg, 1.54 mmol) and after 10 minutes the cooling bath removed  
and stirring continued for 2 hours. The reaction was quenched by the addition of water and  
8195 the mixture diluted with water and extracted with 3 portions of ethyl ether. The combined  
organic fractions were washed with water, brine, dried, filtered and concentrated. The  
residue was purified by column chromatography on silica gel (20 g, 20% ethyl  
acetate/hexane) to provide 158 mg (67%) of the title compound. MS (DCI, NH<sub>3</sub>): 306  
(MH)<sup>+</sup>.



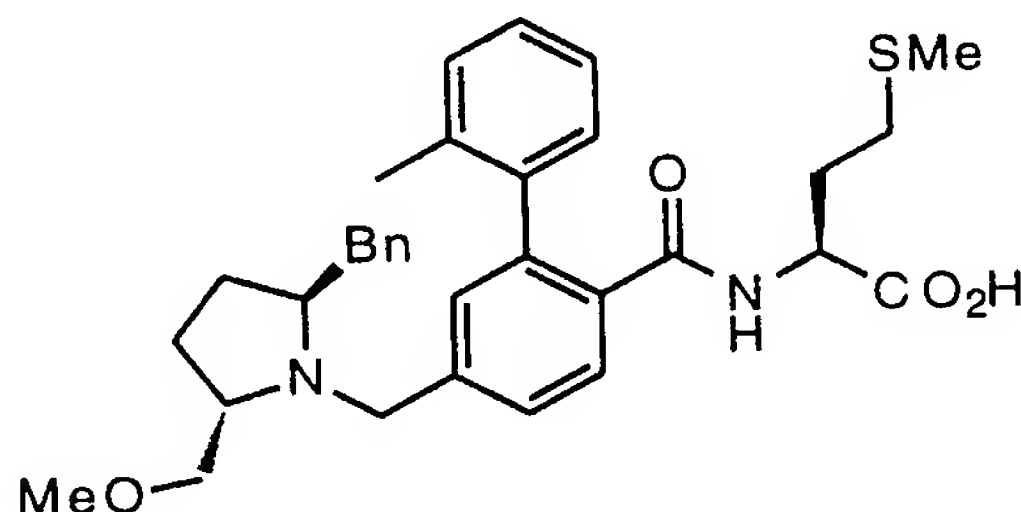
Example 1118E2(S)-methoxymethyl-5-benzylpyrrolidine, hydrochloride salt

8205 Following the procedure of example 1106C, example 1118D (152 mg, 0.5 mmol) provided 110 mg, (91%) of the title compound. MS (DCI, NH<sub>3</sub>): 306 (MH)<sup>+</sup>.

Example 1118F

8210 N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

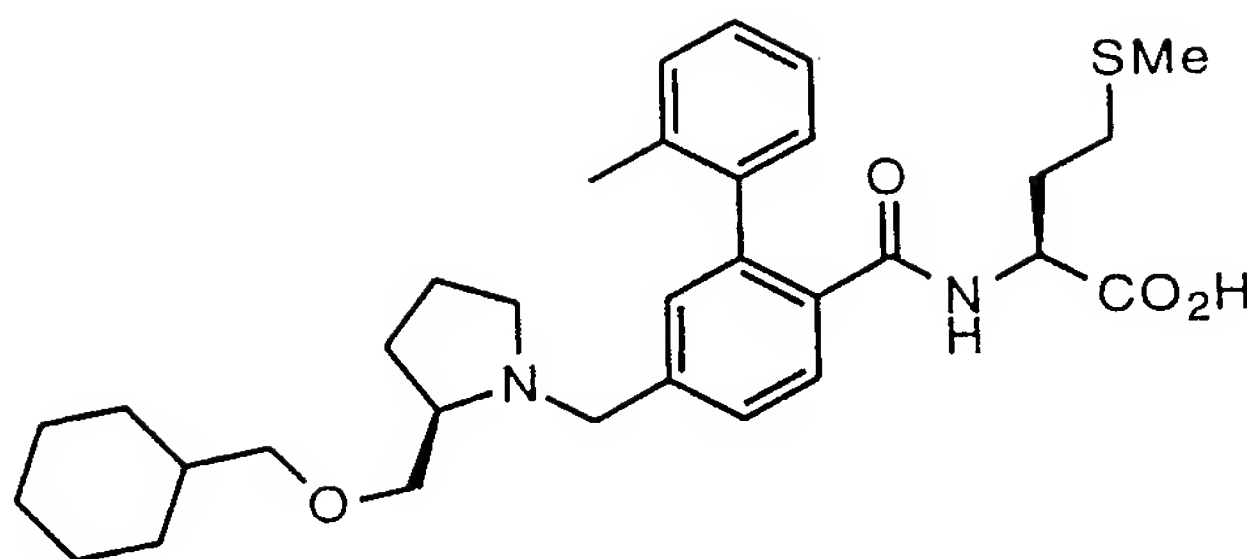
Following the procedure of example 1106D, part 1, example 1118E (106 mg, 0.44 mmol) provided 95 mg (41%) of the title compound. MS (ESI<sup>+</sup>): 575 (MH<sup>+</sup>): (ESI<sup>-</sup>): 573 (M-H).

Example 1118G

8215 N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

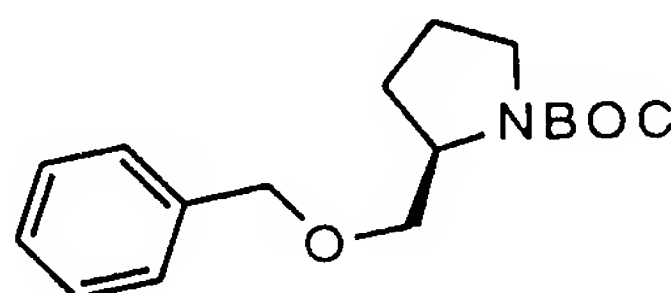
8220 Following the procedure of example 1105D, example 1118F (88 mg, 0.15 mmol) provided 50 mg (60%) of the title compound. <sup>1</sup>H nmr (300 MHz., dmso d<sub>6</sub>): δ 8.11, d, 1H; 7.48, m, 2H; 7.19, m, 8H; 7.03, d, 2H; 4.22, m, 1H; 4.08, d, 1H; 3.93, d, 1H; 3.22, s, 3H; 3.09, m, 2H; 2.94, dd, 1H; 2.37, dd, 1H; 1.99 - .22, m, 4H; 1.97, s, 3H; 1.78, bm, 2H; 1.56, m, 2H; 1.42, m, 2H. MS (ESI<sup>+</sup>): 561 (MH<sup>+</sup>): (ESI<sup>-</sup>): 559 (M-H). Calc'd for C<sub>33</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>S•0.43 H<sub>2</sub>O; C 69.72; H 7.24; N 4.93; Found: C 69.72; H 7.11; N 4.78.



Example 1119

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

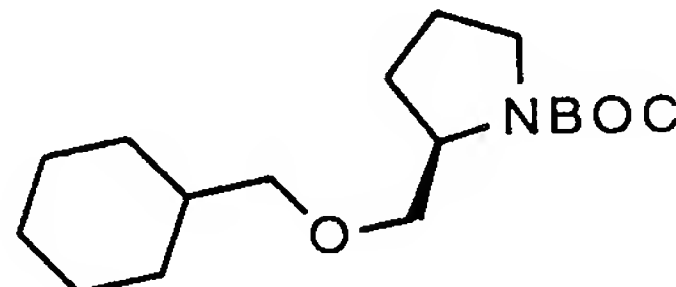
8230

Example 1119A

N-t-Butoxycarbonyl- 2(R)-benzyloxymethylpyrrolidine

8235

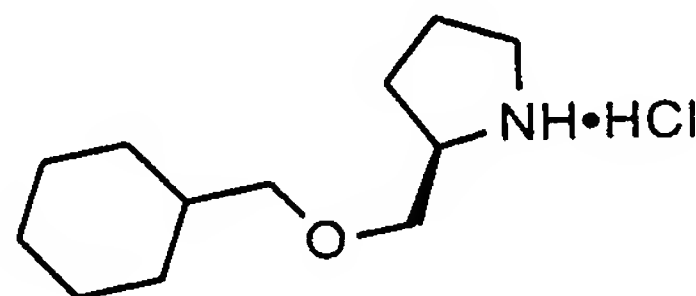
Following the procedure of example 1109F, N-t-butoxycarbonyl-2(R)-hydroxymethylpyrrolidine (1.06 g, 5.00 mmol) provided 1.20 g (82%) of the title compound. MS (DCI, NH<sub>3</sub>): 292 (MH)<sup>+</sup>.

Example 1119B

N-t-Butoxycarbonyl- 2(R)-cyclohexylmethoxymethylpyrrolidine

8240

Following the procedure of example 1109G, example 1119A (0.60 g, 2.06 mmol) provided 0.59 g (97%) of the title compound. MS (DCI, NH<sub>3</sub>): 298 (MH)<sup>+</sup>.

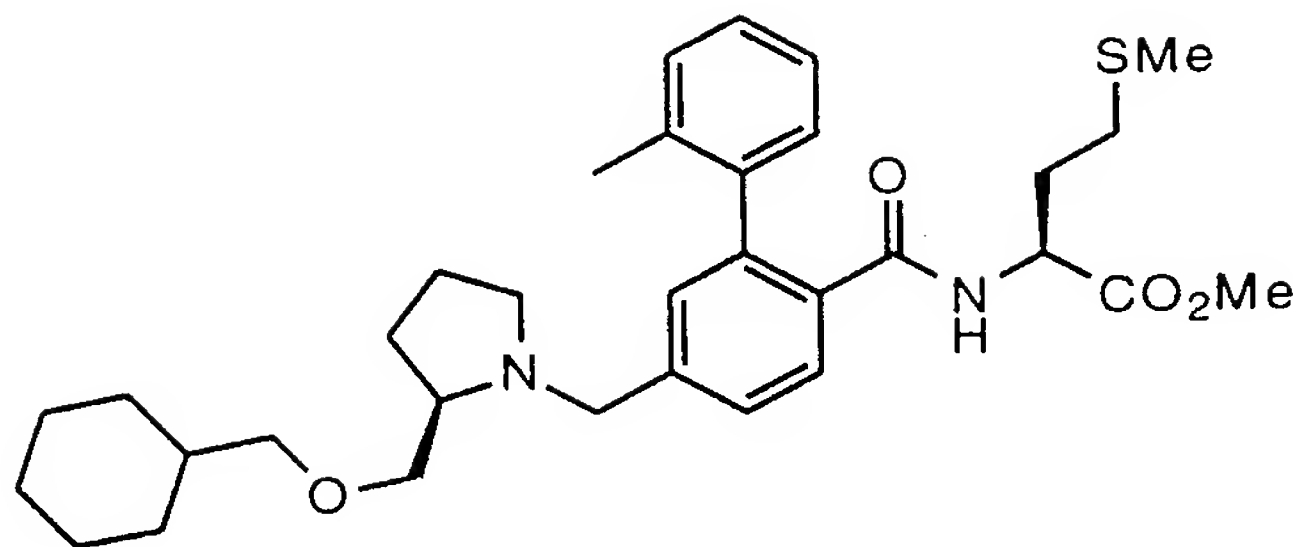
Example 1119C

2(R)-cyclohexylmethoxymethylpyrrolidine, hydrochloride salt

8245

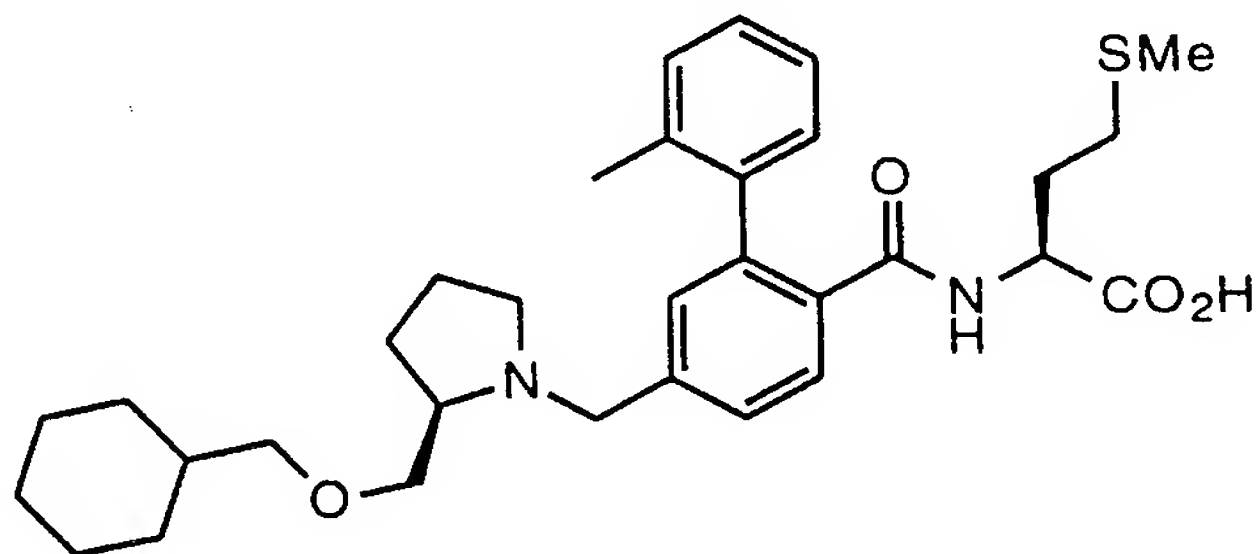
Following the procedure of example 1106C, example 1119B (573 mg, 1.93 mmol) provided 467 mg (100%) of the title compound. MS (DCI, NH<sub>3</sub>): 198 (MH)<sup>+</sup>.

8250

Example 1119D

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

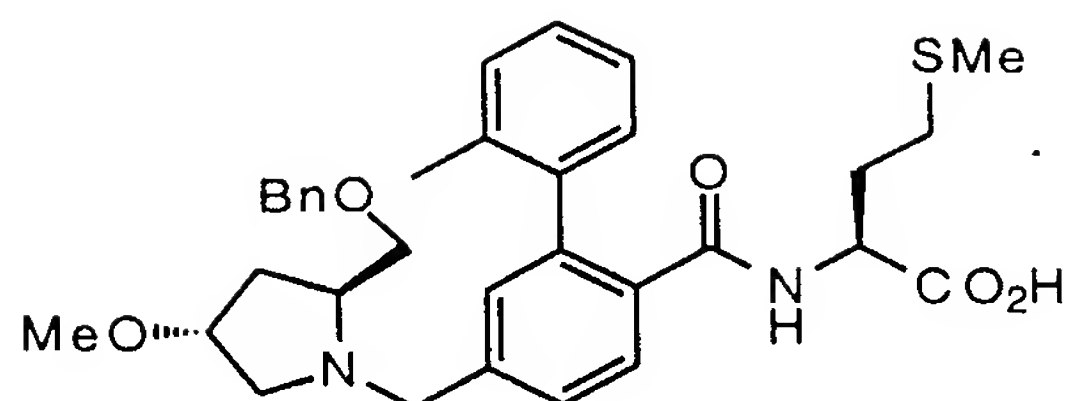
8255 Following the procedure of example 1106C, example 1119C (175 mg, 0.75 mmol) provided 181 mg (64%) of the title compound. MS (ESI+): 567 (MH+); (ESI-): 565 (M-H).

Example 1119E

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

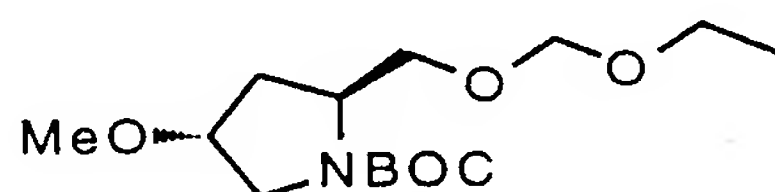
8260 Following the procedure of example 1104D, example 1119D (174 mg, 0.31 mmol) provided 163 mg (95%) of the title compound.. <sup>1</sup>H nmr (300 MHz., dmsd<sub>6</sub>): δ 8.10, d, 1H; 7.47, d, 1H; 7.36, d, 1H; 7.20, m, 2H; 7.11, m, 3H; 4.21, m, 1H; 4.17, d, 1H; 3.48, d, 1H; 3.18, m, 2H; 2.85, m, 1H; 2.76, m, 1H; 1.98 - 2.30, m, 7H; 1.97, s, 3H; 1.70 - 1.90, m, 3H; 1.62, m, 7H; 1.49, m, 2H; 1.10, m, 4H; 0.88, m, 2H. MS (ESI+): 553 (MH+); (ESI-): 551 (M-H). Calc'd for C<sub>32</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>S•0.50 H<sub>2</sub>O; C 68.42; H 8.07; N 4.99; Found: C 68.47; H 7.82; N 4.77.

8270

Example 1120

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

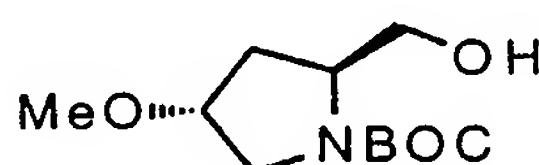
8275

Example 1120A

N-t-Butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-methoxypyrrolidine

8280

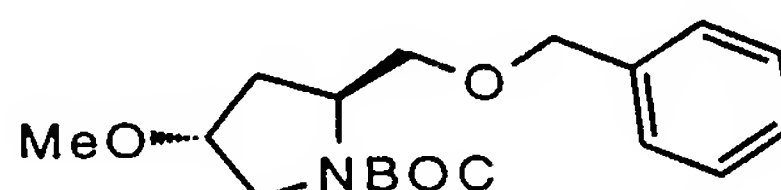
Following the procedure of example 1118D, example 1117C (0.76g, 2.76 mmol) provided 0.64 g (80%) of the title compound. MS (DCI, NH<sub>3</sub>): 290 (MH)<sup>+</sup>.

Example 1120B

8285

N-t-Butoxycarbonyl-2(S)-hydroxymethyl-4(R)-methoxypyrrolidine

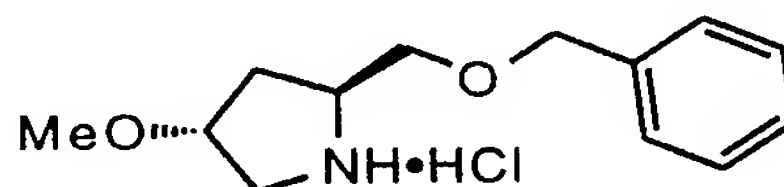
Following the procedure of example 1117F, example 1120A (0.64g, 2.21 mmol) provided 0.39 g (77%) of the title compound. MS (DCI, NH<sub>3</sub>): 232 (MH)<sup>+</sup>.

Example 1120C

8290

N-t-Butoxycarbonyl-2(S)-Benzyloxymethyl-4(R)-methoxypyrrolidine

Following the procedure of example 1109F, example 1120B (0.39 g, 1.68 mmol) provided 0.42 g (78%) of the title compound. MS (DCI, NH<sub>3</sub>): 332 (MH)<sup>+</sup>.

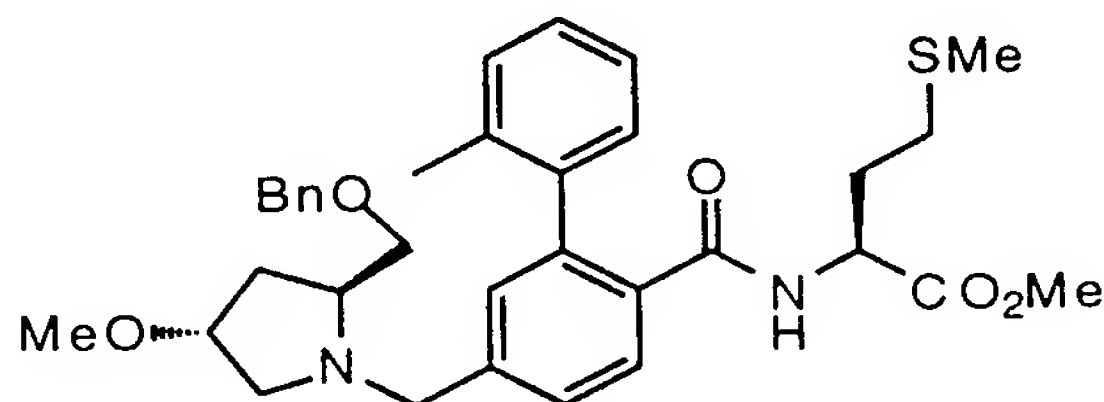
Example 1120D

8295

2(S)-Benzyloxymethyl-4(R)-methoxypyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1120C (0.41 g, 1.28 mmol) provided 0.32 g (97%) of the title compound. MS (DCI, NH<sub>3</sub>): 232 (MH)<sup>+</sup>.

8300

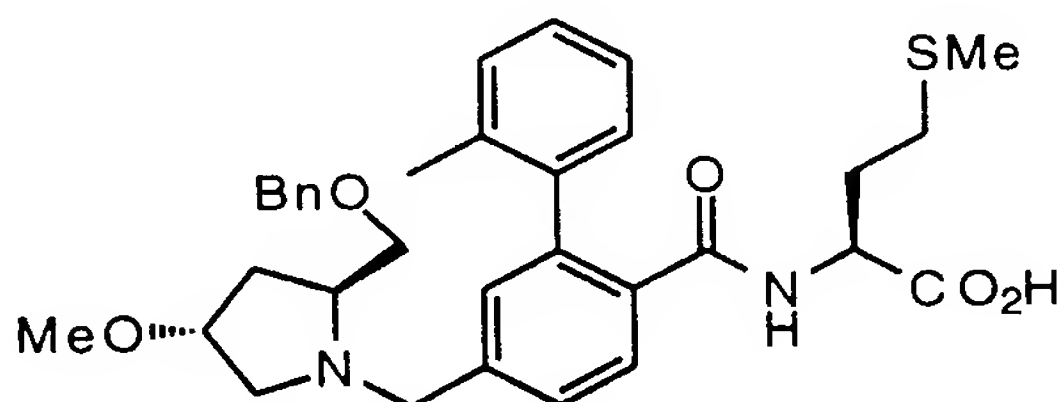


Example 1120E

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8305

Following the procedure of example 1106D, part 1, example 1120D (0.26 g, 1.00 mmol) provided 0.21 g (70%) of the title compound. MS (ESI<sup>+</sup>): 591 (MH<sup>+</sup>): (ESI<sup>-</sup>): 589 (M-H).



Example 1120F

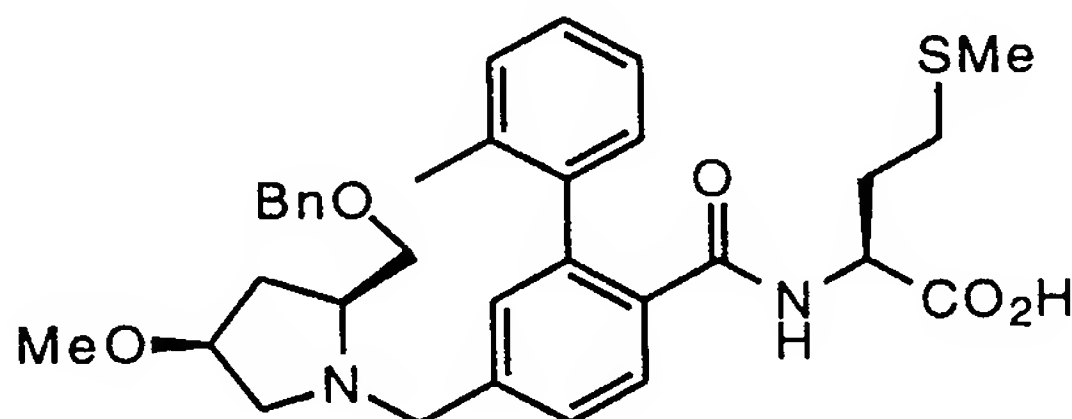
N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8310

Following the procedure of example 1104D, example 1120E (197 mg, 0.33 mmol) provided 163 mg (86%) of the title compound. <sup>1</sup>H nmr (300 MHz., dmso d<sub>6</sub>): δ 8.12, d, 1H; 7.48, d, 1H; 7.36, dd, 1H; 7.27, m, 5H; 7.20, m, 2H; 7.13, m, 3H; 4.48, s, 2H; 4.21, m, 2H; 3.82, m, 1H; 3.53, m, 2H; 3.42, m, 2H; 3.14, s, 3H; 1.99 - 2.30, m, 6H; 1.96, s, 3H; 1.64 - 1.90, m, 4H. MS (ESI<sup>+</sup>): 577 (MH<sup>+</sup>): (ESI<sup>-</sup>): 575 (M-H). Calc'd for C<sub>33</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>S•0.55 H<sub>2</sub>O; C 67.56; H 7.06; N 4.77; Found: C 67.56; H 7.02; N 4.80.

8315

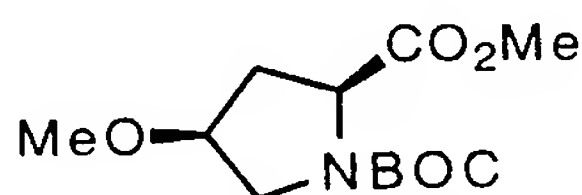
8320



Example 1121

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

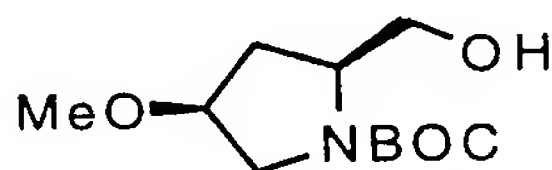
8325



Example 1121A

N-t-Butoxycarbonyl-4(S)-methoxy-L-proline, methyl ester

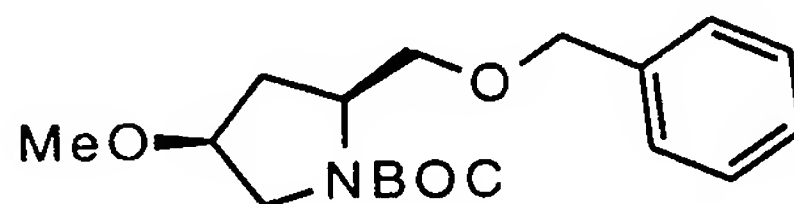
8330 Following the procedure of example 1118D, N-t-butoxycarbonyl-4(S)-hydroxy-L-proline, methyl ester (1.22 g, 5.00 mmol) provided 1.04 g (80%) of the title compound. MS (DCI, NH<sub>3</sub>): 260 (MH<sup>+</sup>); 277 (M+NH<sub>4</sub>)<sup>+</sup>.



Example 1121B

8335 N-t-Butoxycarbonyl-2(S)-hydroxymethyl-4(S)-methoxypyrrolidine

Following the procedure of example 1109E, example 1121A (1.03 g, 3.97 mmol) provided 0.83 g (90%) of the title compound. MS (DCI, NH<sub>3</sub>): 232 (MH<sup>+</sup>).

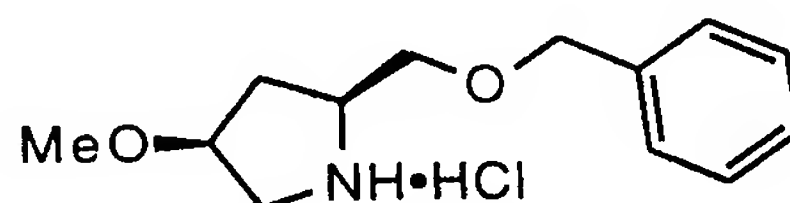


8340

Example 1121C

N-t-Butoxycarbonyl-2(S)-benzyloxymethyl-4(S)-methoxypyrrolidine

Following the procedure of example 1109F, example 1121B (0.41 g, 1.78 mmol) provided 0.46 g (80%) of the title compound. MS (DCI, NH<sub>3</sub>): 322 (MH<sup>+</sup>).



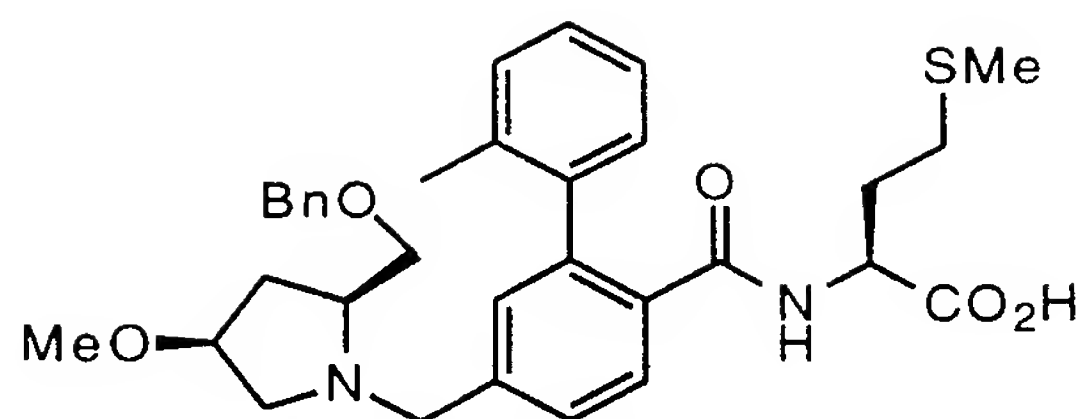
8345

Example 1121D

2(S)-benzyloxymethyl-4(S)-methoxypyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1121C (228 mg, 0.71 mmol) provided 183 mg (100%) of the title compound. MS (DCI, NH<sub>3</sub>): 222 (MH<sup>+</sup>).

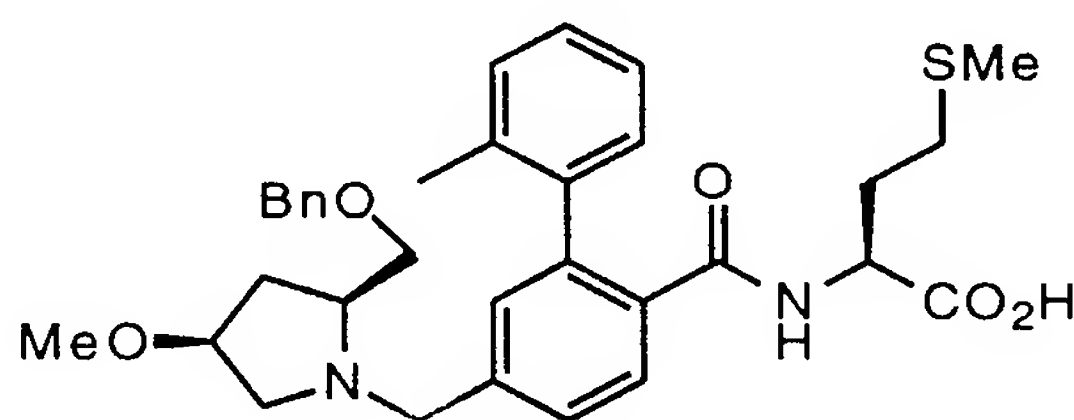
8350



Example 1121E

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8355 Following the procedure of example 1106D, part 1, example 1121D (178 mg, 0.69 mmol) provided 210 mg (71%) of the title compound. MS (ESI+): 591 (MH+); (ESI-): 589 (M-H).

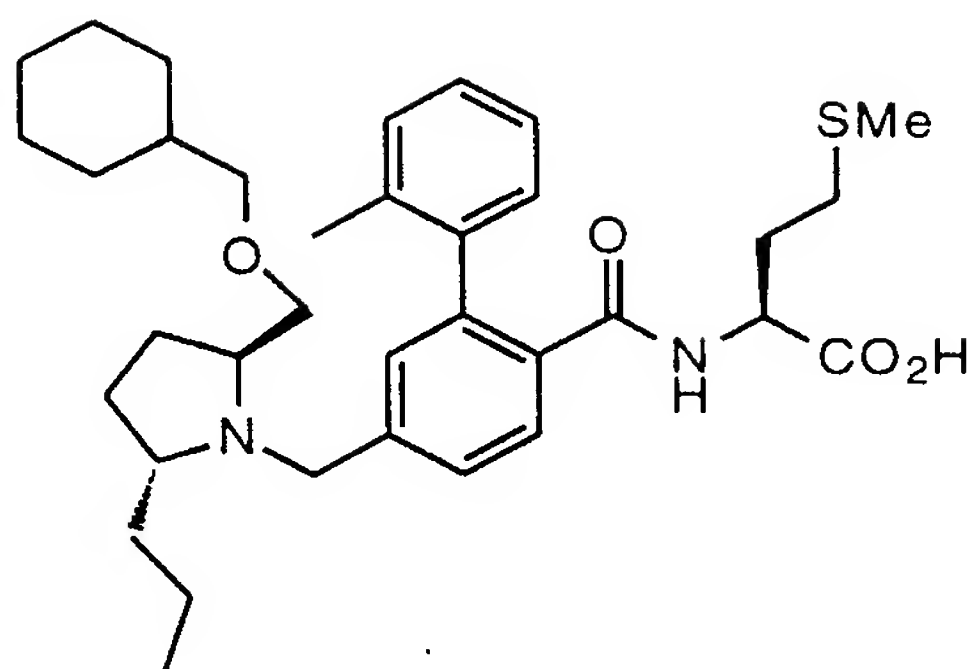


Example 1121F

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

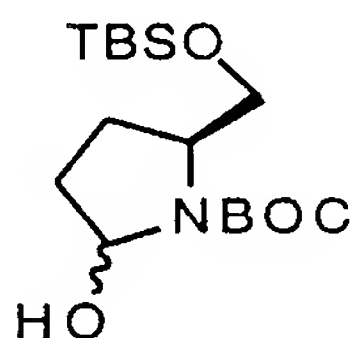
8365 Following the procedure used in example 1104D, example 1121E (204 mg, 0.34 mmol) provided 195 mg (99%) of the title compound. <sup>1</sup>H nmr (300 MHz., dmso d6): δ 8.08, d, 1H; 7.45, d, 1H; 7.33, d, 1H; 7.28, m, 5H; 7.21, m, 2H; 7.14, m, 3H; 4.49, s, 2H; 4.22, m, 1H; 4.18, m, 1H; 3.79, m, 1H; 3.56, dd, 1H; 3.43, dd, 1H; 3.09, s, 3H; 2.90, d, 1H; 2.75, m, 1H; envelope 1.99 - 2.35, 11H; 1.97, s, 3H; 1.78, bm, 2H; 1.51, ddd, 1H. MS (ESI+): 577 (MH+); (ESI-): 575 (M-H). Calc'd for C<sub>33</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>S•0.45 H<sub>2</sub>O; C 67.77; H 7.05; N 4.79; Found: C 67.80; H 6.93; N 4.62.

8370

Example 1122

N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8375

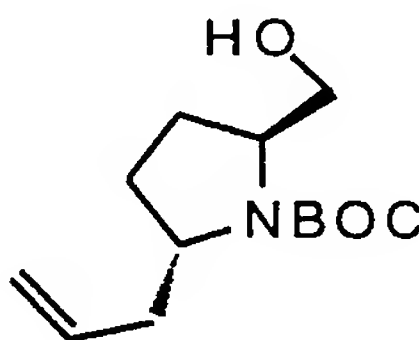
Example 1122A

N-t-Butoxycarbonyl-2(R,S)-hydroxy-5(S)-t-butyltrimethylsilyloxymethylpyrrolidine

8380 Example 1118B (3.10 g, 9.36 mmol) was dissolved in 20 mL of toluene and cooled in a dry ice/acetone bath. The cold solution was treated with diisobutylaluminum hydride (9.4 mL of a 1.5M toluene solution, 14.0 mmol), the dry ice bath was removed and the mixture stirred for 2 hours. The mixture was cooled in an ice/acetone bath and quenched by the careful addition of 10 mL of a 10% methanol/toluene solution. After the cessation of

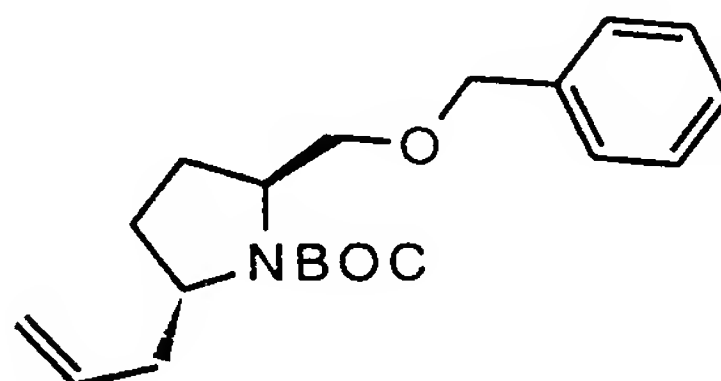
8385 bubbling, the mixture was treated with 75 mL of 1N aqueous HCl and 100 mL of ether and vigorously stirred for 30 minutes and poured into a separatory funnel. The layers were separated and the aqueous layer was extracted with 2 portions of ether and the combined organic fractions were washed with 1N HCl, water and brine, dried, filtered and concentrated to provide 2.93 g (94%) of the title compound. MS (DCI, NH<sub>3</sub>): 332 (MH<sup>+</sup>);

8390 314 (M+NH<sub>4</sub>)<sup>+</sup> - H<sub>2</sub>O.

Example 1122B

N-t-Butoxycarbonyl-5(S)-allyl-2(S)-hydroxymethylpyrrolidine

8395 A solution of example 1122A (663 mg, 2 mmol) and allyltrimethylsilane (1.2 mL, 8 mmol) in 12 mL methylene chloride was cooled in a dry ice/acetone bath and treated with boron trifluoride etherate (0.49 mL, 4.00 mmol) dropwise. The solution was stirred for 30 minutes and then the dry ice bath was replaced with an ice/acetone bath and the mixture stirred an additional 30 minutes and quenched by the addition of 2M sodium carbonate. The  
8400 mixture was diluted with water and methylene chloride and the layers separated. The aqueous phase was extracted with 2 additional portions of methylene chloride and the combined organic fractions were dried, filtered and concentrated. The residue was dissolved in 4 mL of THF and treated with TBAF (4 mL of a 1.0M THF solution, 4 mmol) and the mixture stirred overnight. The reaction was partitioned between water and 3 portions of  
8405 ethyl acetate. The combined organic extracts were washed with water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (25 g, 30% ethyl acetate/hexanes) to provide 227 mg (47%) of the title compound. MS (DCI, NH<sub>3</sub>): 242 (MH<sup>+</sup>).



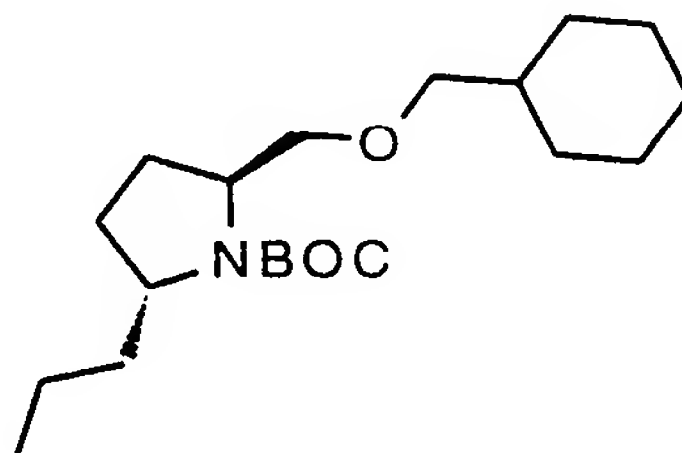
8410

Example 1122C

N-t-Butoxycarbonyl-5(S)-allyl-2(S)-benzyloxymethylpyrrolidine

Following the procedure of example 1109F, example 1122B (223 mg, 0.92 mmol) provided 250 mg (82%) of the title compound. (DCI, NH<sub>3</sub>): 332 (MH<sup>+</sup>).

8415

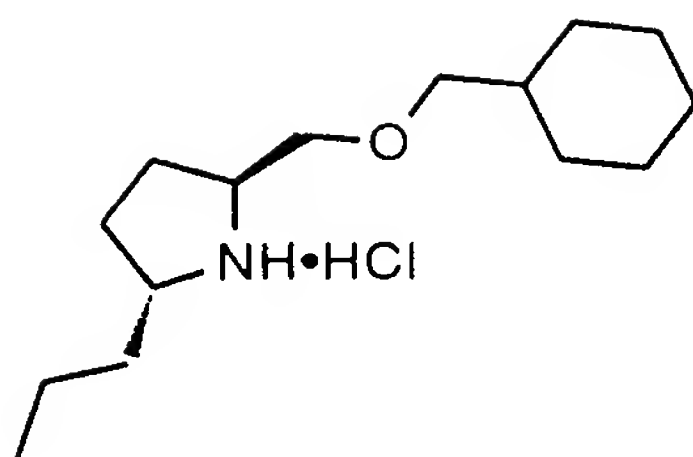


Example 1122D

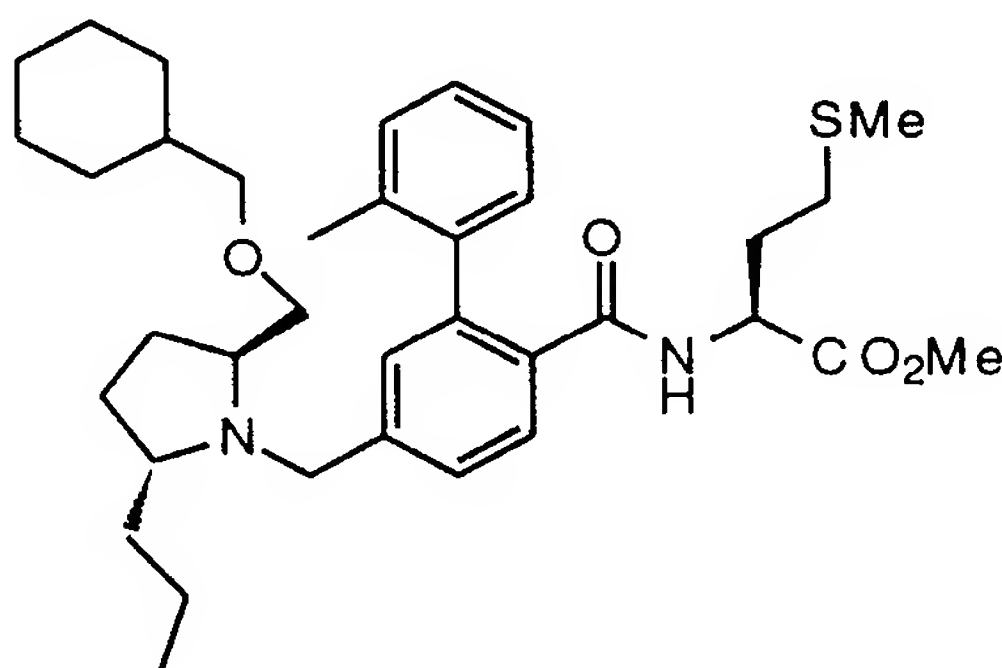
N-t-Butoxycarbonyl-5(R)-propyl-2(S)-cyclohexylmethyloxymethylpyrrolidine

8420 Following the procedure of example 1109G, example 1122C (245 mg, 0.74 mmol) provided 246 mg (100%) of the title compound. (DCI, NH<sub>3</sub>): 340 (MH<sup>+</sup>).



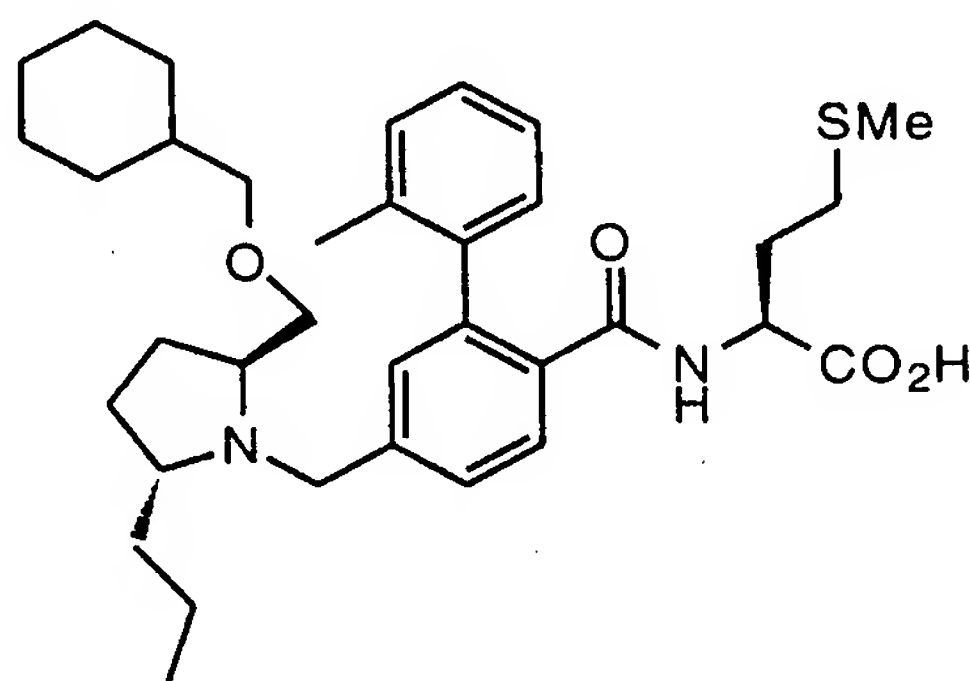
Example 1122E5(R)-propyl-2(S)-cyclohexylmethyloxymethylpyrrolidine, hydrochloride salt

8425 Following the procedure of example 1106C, example 1122D (245 mg, 0.74 mmol) provided 204 mg (100%) of the title compound. (DCI, NH<sub>3</sub>): 240 (MH<sup>+</sup>).

Example 1122F

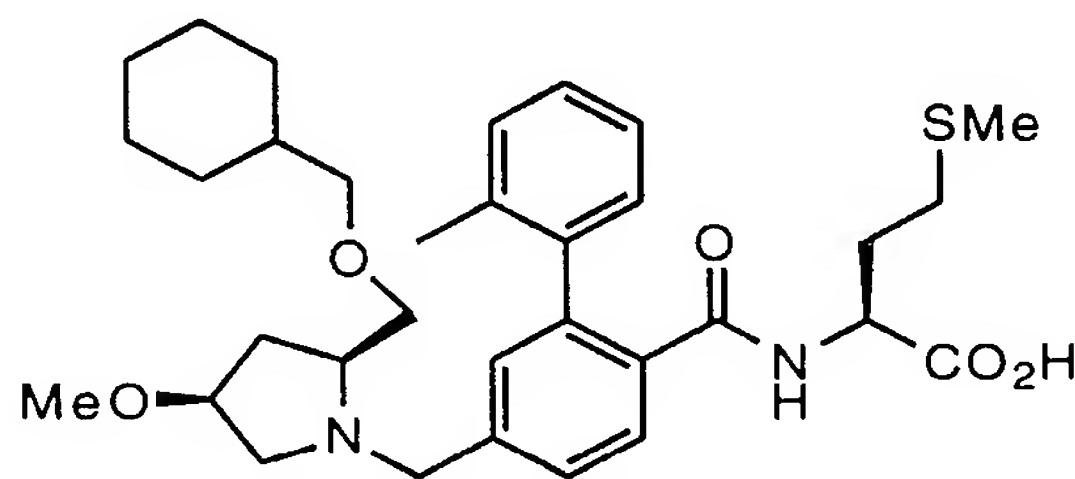
8430 N-[4-(2(S)-cyclohexylmethyloxymethyl-5(R)-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1106D, part 1, example 1122E (204 mg, 0.74 mmol) provided 110 mg (36%) of the title compound. MS (ESI<sup>+</sup>): 609 (MH<sup>+</sup>): (ESI<sup>-</sup>): 607 (M-H).

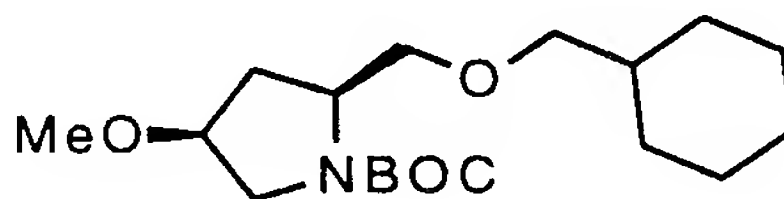
Example 1122G

8435 N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8440 Following the procedure of example 1104D, example 1122F (104 mg, 0.17 mmol) provided 87 mg (86%) of the title compound. <sup>1</sup>H nmr (300 MHz., dmso d6): δ 8.04, d, 1H; 7.46, d, 1H; 7.35, d, 1H; 7.20, m, 2H; 7.13, m, 3H; 4.22, m, 1H; 3.83, dd, 2H; 3.08, m, 2H; 3.04, d, 2H; 2.88, pentet, 1H; 2.63, m, 1H; 1.99 - 2.24, m, 6H; 1.96, s, 3H; 1.77, bm, 4H; 1.59, m, 6H; envelope 1.00 - 1.55, 11H; 0.81, m, 5H. MS (ESI+): 595 (MH+);  
 8445 (ESI-): 593 (M-H). Calc'd for C<sub>35</sub>H<sub>50</sub>N<sub>2</sub>O<sub>4</sub>S•0.55 H<sub>2</sub>O; C 69.51; H 8.52; N 4.63; Found: C 69.54; H 8.32; N 4.58.

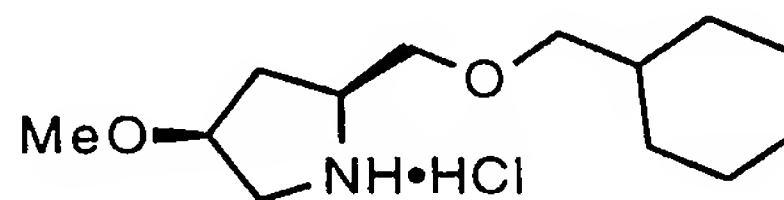


8450 Example 1123  
N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine



8455 Example 1123A  
N-t-Butoxycarbonyl-2(S)-cyclohexylmethyloxymethyl-4(S)-methoxypyrrolidine

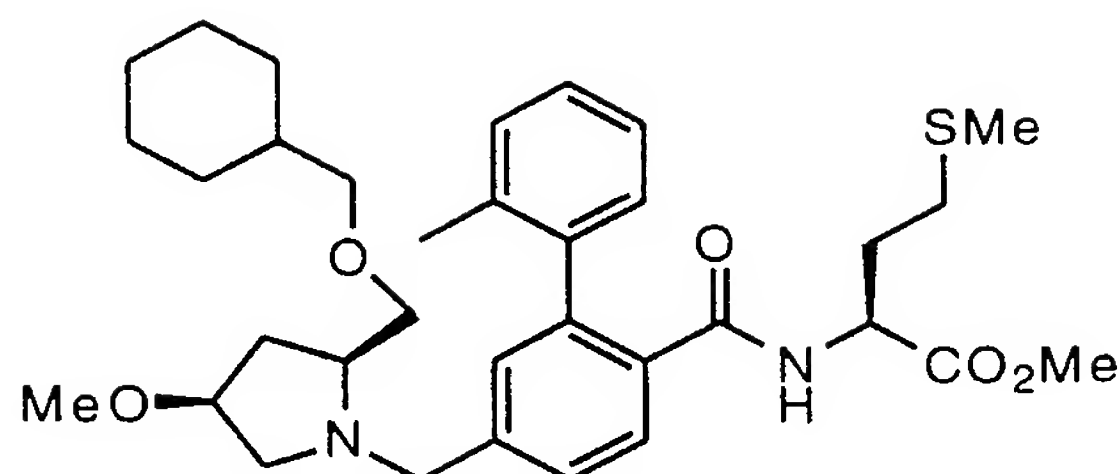
Following the procedure of example 1109G, example 1112C (227 mg, 0.71 mmol) provided 232 (100%) of the title compound. (DCI, NH<sub>3</sub>): 328 (MH<sup>+</sup>).



8460 Example 1123B  
2(S)-cyclohexylmethyloxymethyl-4(S)-methoxypyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1123 A (232 mg, 0.71 mmol) provided 187 mg (100%) of the title compound. (DCI, NH<sub>3</sub>): 228 (MH<sup>+</sup>).

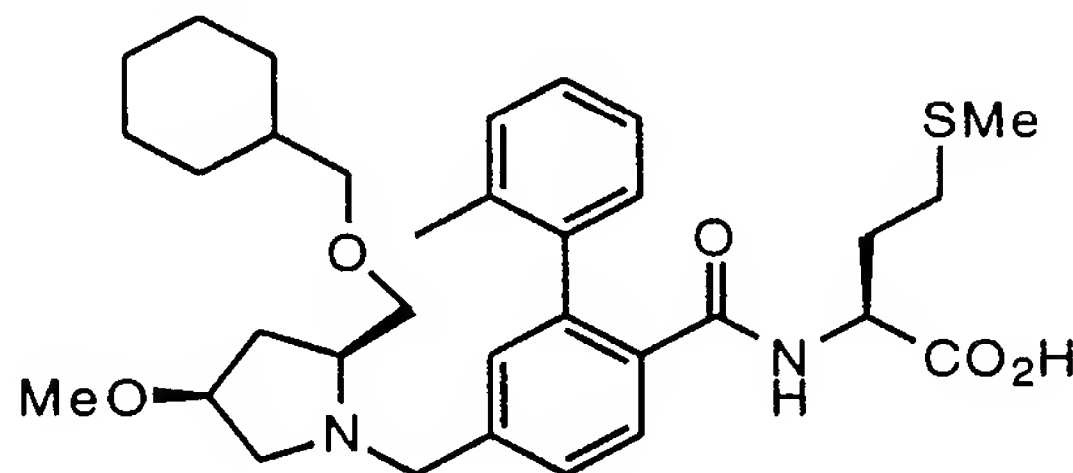
8465



Example 1123C

N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8470 Following the procedure of example 1106D, part 1, example 1123B (181 mg, 0.69 mmol) provided 196 mg (66%) of the title compound. MS (ESI+): 597 (MH+); (ESI-): 595 (M-H).



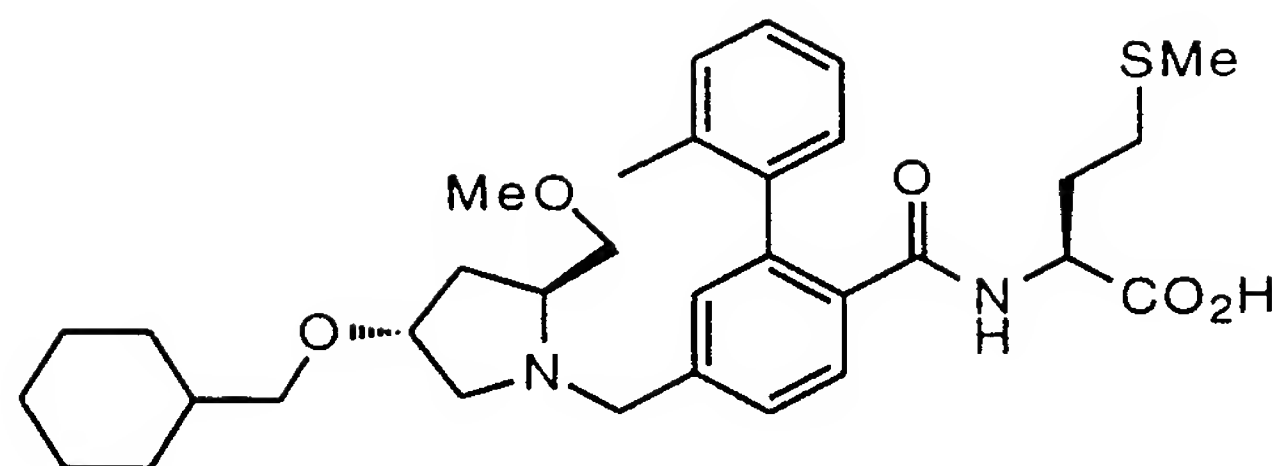
Example 1123D

N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8475 Following the procedure of example 1104D, example 1123C (190 mg, 0.32 mmol) provided 174 mg (93%) of the title compound. <sup>1</sup>H nmr (300 MHz., dmso d6): δ 8.12, d, 1H; 7.46, d, 1H; 7.35, dd, 1H; 7.19, m, 2H; 7.13, m, 3H; 4.18, m, 2H; 3.78, m, 1H; 3.45, dd, 1H; 3.29, d, 1H; 3.17, dd, 1H; 3.15, dd, 1H; 3.08, s, 3H; 2.89, bd, 1H; 2.72, m, 1H; 2.29, m, 1H; envelope 1.97 - 2.25, 6H; 1.96, s, 3H; 1.77, bm, 2H; 1.62, m, 5H; 1.47, m, 2H; 1.12, m, 3H; 0.86, bq, 2H. MS (ESI+): 583 (MH+); (ESI-): 581 (M-H). Calc'd for C<sub>33</sub>H<sub>46</sub>N<sub>2</sub>O<sub>5</sub>SH<sub>2</sub>O; C 68.01; H 7.96; N 4.81; Found: C 67.96; H 7.96; N 4.81.

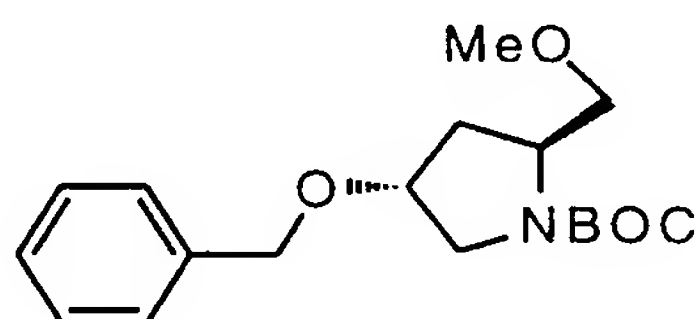
8480

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Example 1124

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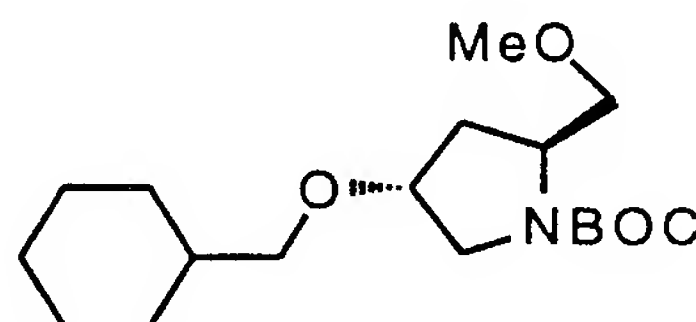
N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Example 1124A

8495

N-t-Butoxycarbonyl-2(S)-methoxymethyl-4(S)-benzyloxypyrrolidine

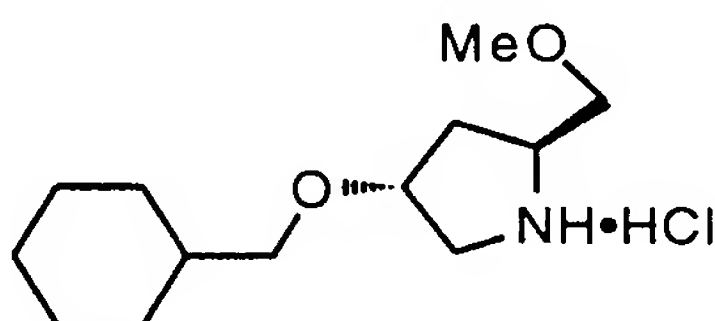
Following the procedure of example 1118D, example 1117A (922 mg, 3.00 mmol) provided 0.64 g (67%) of the title compound. (DCI, NH<sub>3</sub>): 322 (MH<sup>+</sup>).

Example 1124B

8500

N-t-Butoxycarbonyl-2(S)-methoxymethyl-4(S)-cyclohexylmethyloxypyrrolidine

Following the procedure of example 1109G, example 1124A (0.63 g, 1.96 mmol) provided 0.63 g (99%) of the title compound. (DCI, NH<sub>3</sub>): 328 (MH<sup>+</sup>).

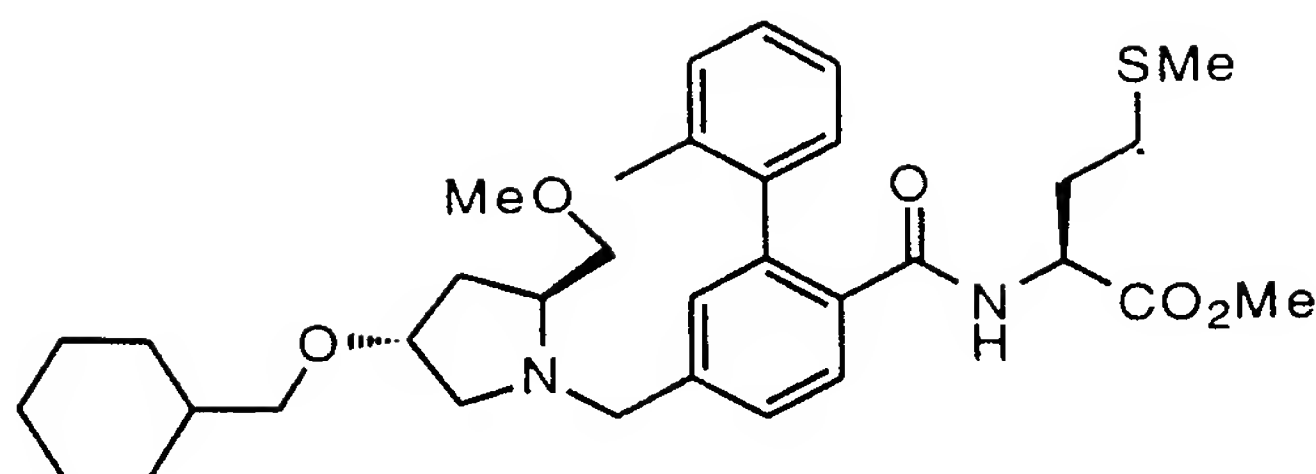
Example 1124C

8505

2(S)-methoxymethyl-4(S)-cyclohexylmethyloxypyrrolidine, hydrochloride salt

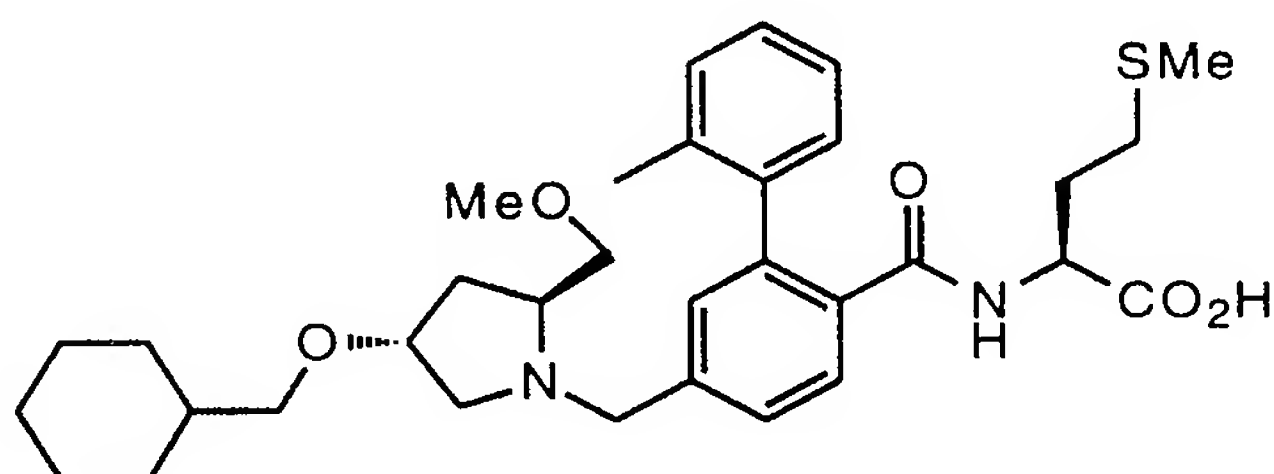
Following the procedure of example 1106C, example 1124B (627 mg, 1.91 mmol) provided 511 mg (101%) of the title compound. (DCI, NH<sub>3</sub>): 228 (MH<sup>+</sup>).

8510

Example 1124D

N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

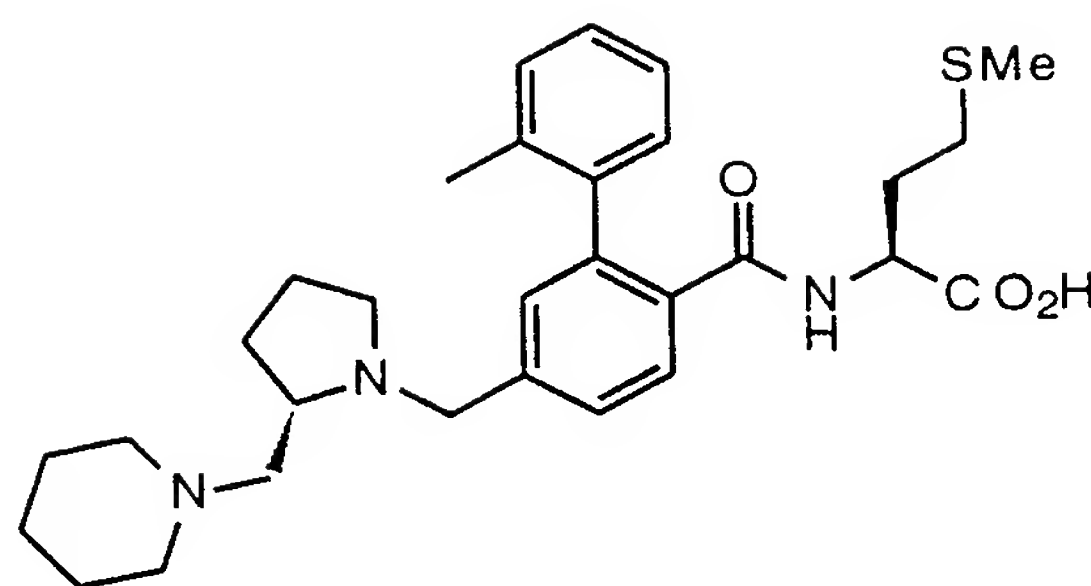
8515 Following the procedure of example 1106D, part 1, example 1124C (264 mg, 1.50 mmol) provided 209 mg (70%) of the title compound. MS (ESI+): 597 (MH+); (ESI-): 595 (M-H).

Example 1124E

N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

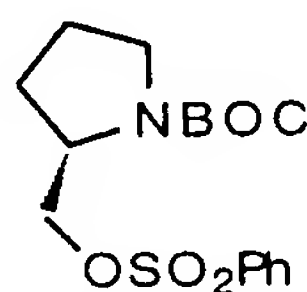
8520 Following the procedure of example 1104D, example 1124D (197 mg, 0.33 mmol) provided 176 mg (92%) of the title compound. <sup>1</sup>H nmr (300 MHz., dmsO d6): δ 8.14, d, 1H; 7.47, d, 1H; 7.38, d, 1H; 7.22, m, 2H; 7.13, m, 3H; 4.23, m, 1H; 4.13, bd, 1H; 3.87, m, 1H; 3.55, bm, 1H; 3.42, dd, 2H; 3.27, dd, 1H; 3.23, s, 3H; 3.11, dd, 1H; ; envelope 1.98 - 2.24, 6H; 1.96, s, 3H; envelope 1.55 - 1.93, 8H; 1.43, bm, 1H; 1.12 - 1.30, m, 4H; 0.86. bq, 2H. MS (ESI+): 583 (MH+); (ESI-): 581 (M-H). Calc'd for C<sub>33</sub>H<sub>46</sub>N<sub>2</sub>O<sub>5</sub>S•0.50 H<sub>2</sub>O; C 66.97; H 8.00; N 4.73; Found: C 67.04; H 7.97; N 4.51.

8530

Example 1125

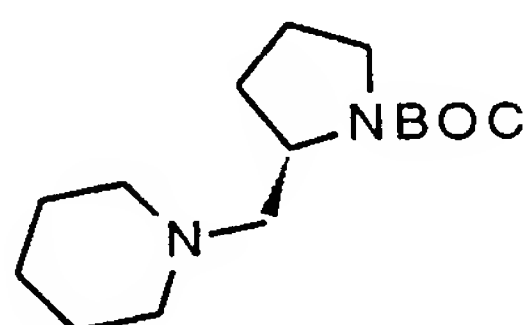
N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8535

Example 1125AN-t-Butoxycarbonyl-2(S)-phenylsulfonyloxymethylpyrrolidine

8540 A solution of N-t-Butoxycarbonyl-2(S)-hydroxymethylpyrrolidine (2.01 g, 10.00 mmol) and triethyl amine (1.70 mL, 12.00 mmol) in 10 mL of methylene chloride was cooled in an ice bath and treated with benzenesulfonylchloride (1.96 g, 11.00 mmol) and the mixture placed in a refrigerator overnight. The mixture was allowed to reach room temperature and partitioned between ethyl ether and water. The aqueous phase was extracted with ether and the combined organic layers washed with water 1N HCl, saturated sodium bicarbonate, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (120 g, 25% ethyl acetate/hexanes) to provide 2.82 g (83%) of the title compound. MS (DCI, NH<sub>3</sub>): 359 (M+NH<sub>4</sub>)<sup>+</sup>.

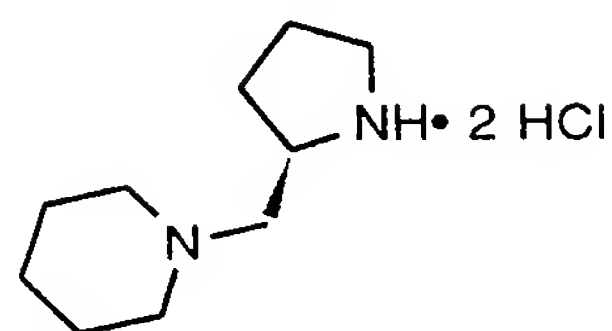
8545

Example 1125BN-t-Butoxycarbonyl-2(S)-piperidinylmethylpyrrolidine

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8555 Example 1125B (341 mg, 1.00 mmol) was dissolved in 1 mL of piperidine and the mixture heated in a screw-cap vial to 100°C for 16 hours. The mixture was cooled to room temperature and concentrated. The residue was partitioned between water and 3 portions of ethyl acetate. The combined organic layers were washed with water, brine, dried filtered

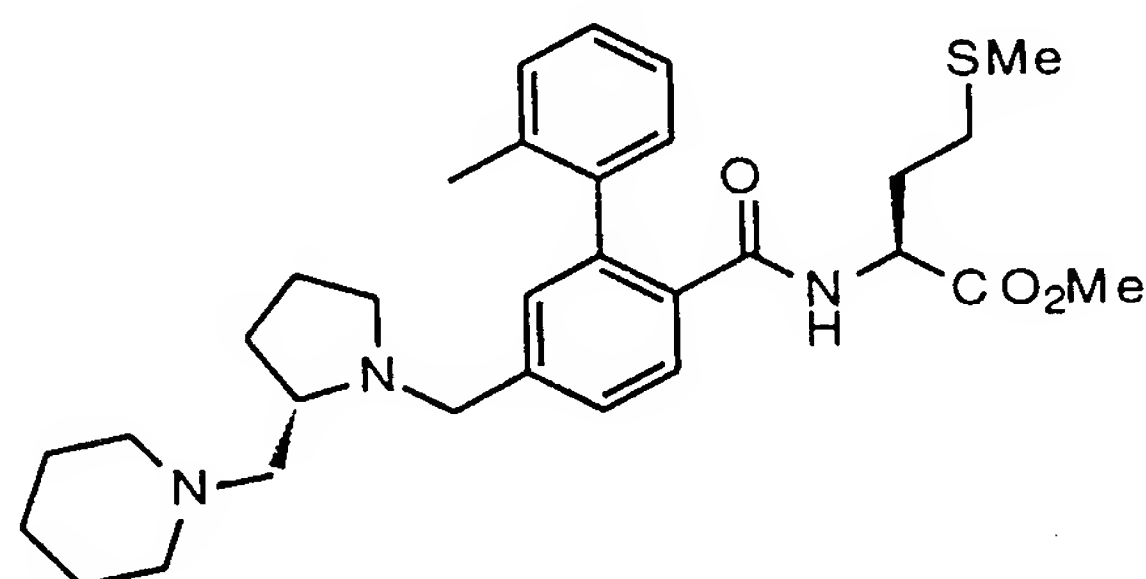
and concentrated to provide 234 mg (87%) of the title compound. (DCI, NH<sub>3</sub>): 269 (MH<sup>+</sup>).



8560

Example 1125C2(S)-piperidinylmethylpyrrolidine, methyl ester

Using the procedure of example 1106C, example 1125C (230 mg, 0.85 mmol) provided 195 mg (100%) of the title compound. (DCI, NH<sub>3</sub>): 159 (MH<sup>+</sup>).

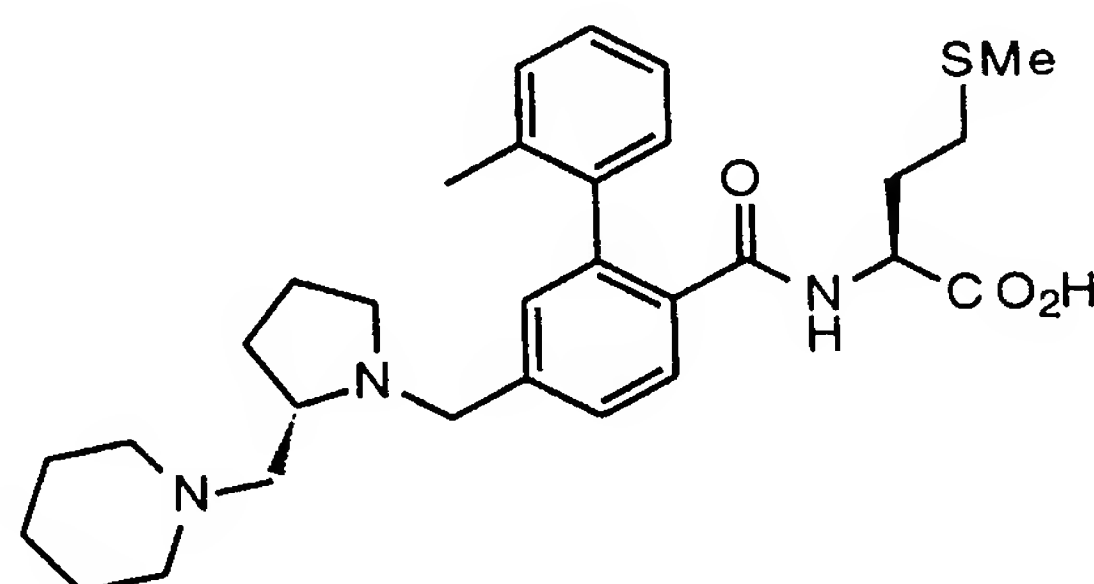


8565

Example 1125DN-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Using the procedure described in example 1106D, part 1, example 1125C (195 mg, 0.86 mmol) provided 206 mg (77%) of the title compound. MS (ESI<sup>+</sup>): 538 (MH<sup>+</sup>); (ESI<sup>-</sup>): 536 (M-H).

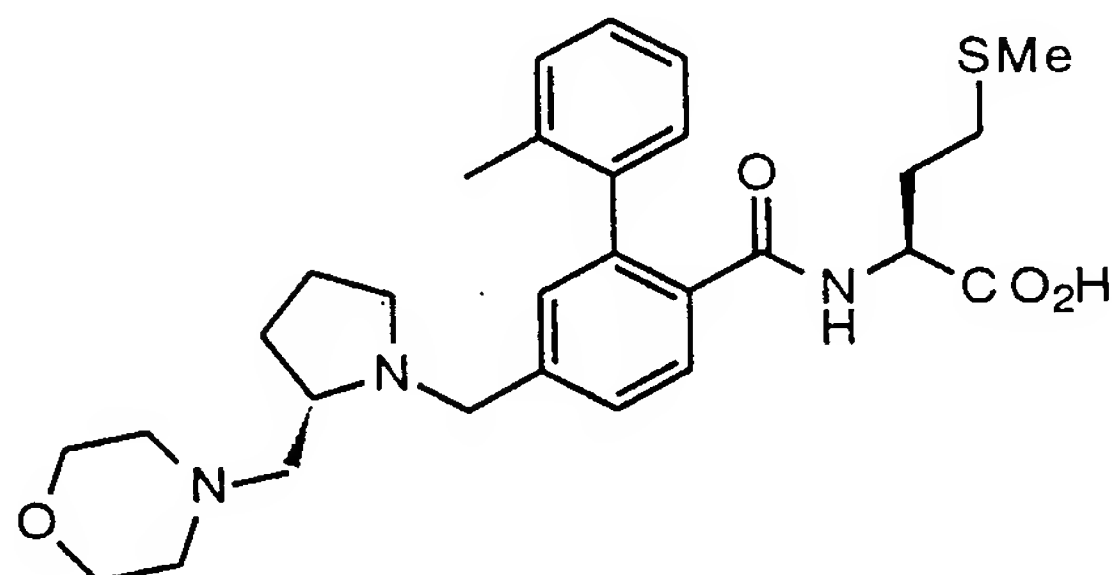
8570

Example 1125EN-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1125D (195 mg, 0.36 mmol) provided 117 mg of the title compound. <sup>1</sup>H nmr (300 MHz., dmso d<sub>6</sub>): δ 8.12, d, 1H;

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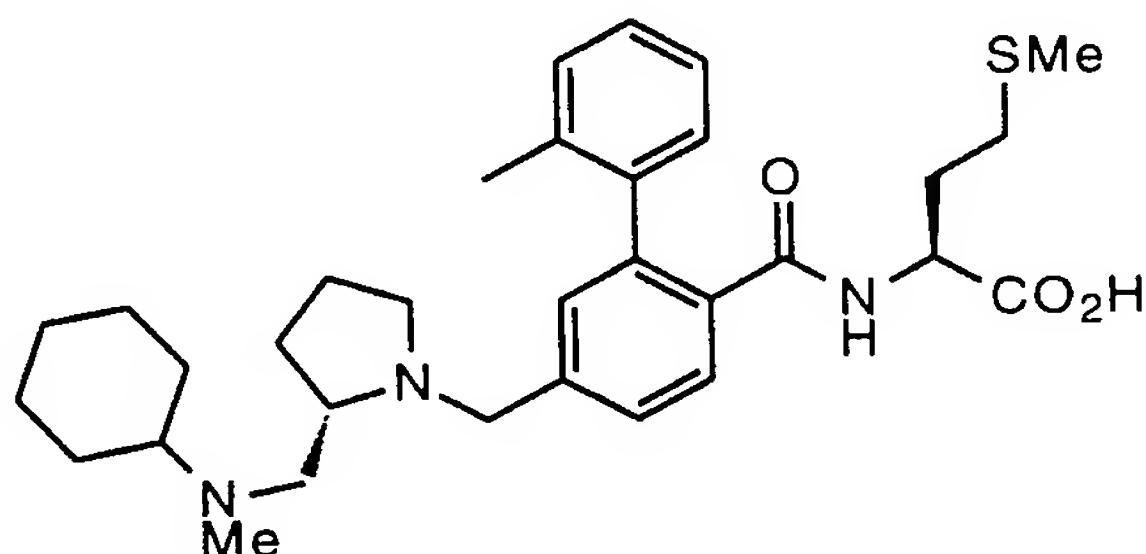
7.51, d, 1H; 7.43, d, 1H; 7.21, m, 2H; 7.14, m, 3H; 4.22, m, 2H; 3.55, d, 1H; 3.06, m, 1H; 2.90, m, 6H; 2.75, m, 1H; 2.41, m, 1H; 1.97 - 2.24, m, 6H; 1.96, s, 3H; 1.74, bm, 4H; 1.62, m, 4H; 1.45, m, 2H. MS (ESI+): 524 (MH+); (ESI-): 522 (M-H). Calc'd for  $C_{30}H_{41}N_3O_3S \cdot 0.65 H_2O \cdot 1.00 TFA$ ; C 59.50; H 6.77; N 6.71; Found: C 60.10; H 6.89; N 6.46.



#### Example 1126

N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared according to the procedure of example 1125 by substituting morpholine for piperidine in example 1125B.  $^1H$  nmr (300 MHz., dmso d6):  $\delta$  8.17, d, 1H; 7.53, d, 1H; 7.48, d, 1H; 7.28, m, 1H; 7.23, m, 2H; 7.15, m, 2H; 4.39, d, 1H; 4.23, m, 1H; envelope 3.00 - 3.90, 5H; 2.58, m, 1H; 2.51, m, 3H; 2.42, m, 4H; 1.97 - 2.24, m, 6H; 1.96, s, 3H; 1.79, bm, 3H; 1.62, m, 1H. MS (ESI+): 524 (MH+); (ESI-): 526 (M-H). Calc'd for  $C_{29}H_{39}N_3O_4S \cdot 0.65 H_2O \cdot 0.55 TFA$ ; C 60.24; H 6.86; N 7.00; Found: C 60.26; H 6.94; N 6.87.



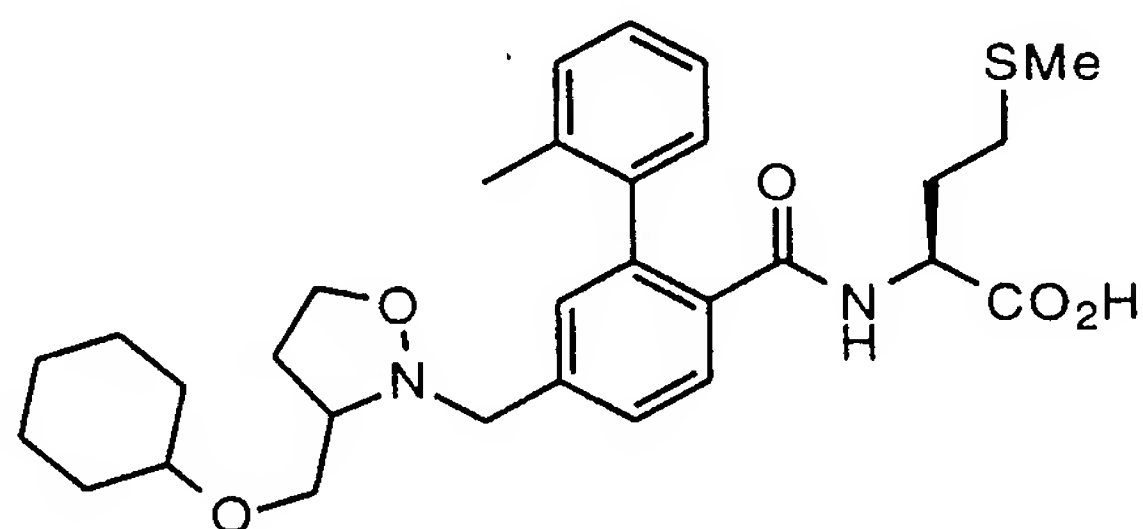
#### Example 1127

N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared according to the procedure of example 1125 by substituting N-methylcyclohexylamine for piperidine in example 1125B.  $^1H$  nmr (300 MHz., dmso d6):  $\delta$

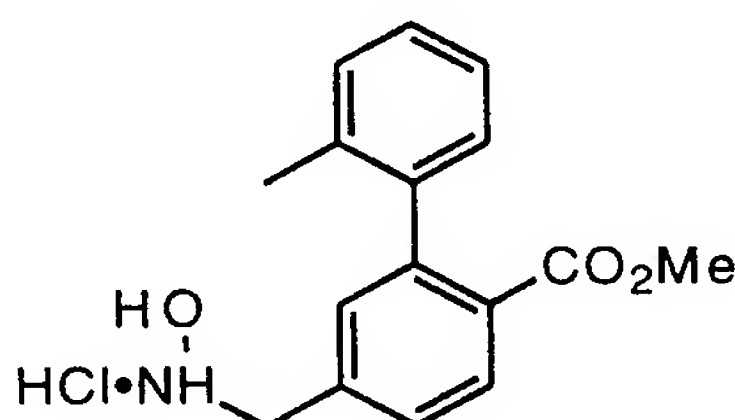


8.00, d, 1H; 7.49, d, 1H; 7.40, d, 1H; 7.20, m, 3H; 7.13, m, 2H; 4.22, m, 1H; 4.18, d, 1H; 3.47, d, 1H; envelope 2.60 - 2.95, 3H; 2.50, s, 3H; 2.42, s, 2H; 2.33, m, 1H; envelope 1.90 - 2.22, 6H; 1.96, s, 3H; 1.75, bm, 6H; 1.56, m, 2H; envelope 0.95 - 1.35, 6H. MS (ESI+): 552 (MH+); (ESI-): 550 (M-H). Calc'd for C<sub>32</sub>H<sub>45</sub>N<sub>3</sub>O<sub>3</sub>S•0.75 H<sub>2</sub>O•0.50 TFA; C 63.69; H 7.61; N 6.75; Found: C 63.69; H 7.66; N 6.67.



Example 1130

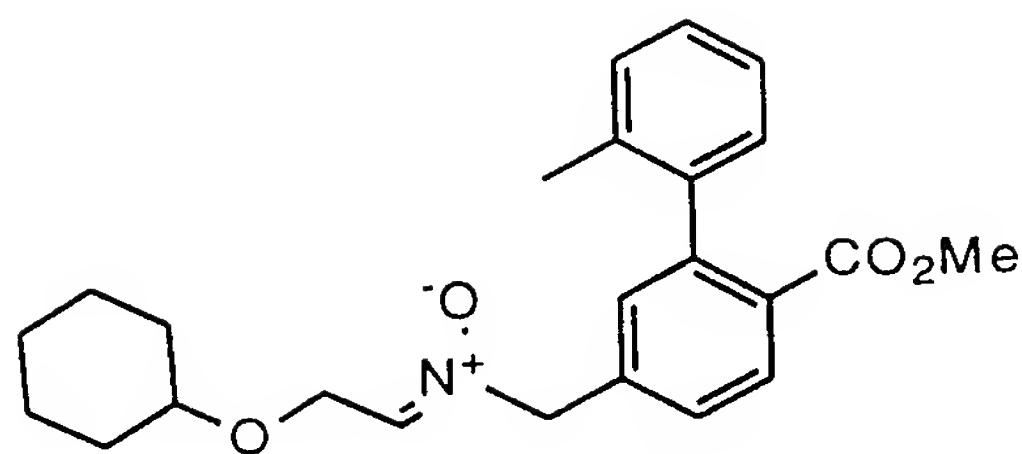
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine



Example 1130A

4-N-Hydroxyaminomethyl-2-(2-methylphenyl)benzoic acid, methyl ester

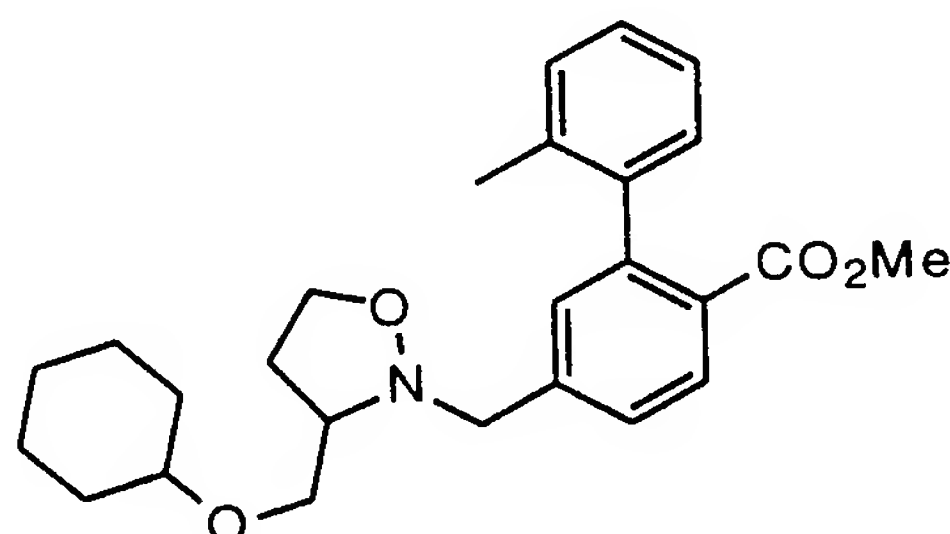
A solution of example 1178D (1.76 g (5.50 mmol) and N,O-bis-t-butoxycarbonylhydroxylamine (1.09 g, 5.00 mmol) in 10 mL of DMF were cooled in an ice bath and treated with sodium hydride (60%, 0.24 g, 6.00 mmol). After stirring for 4 hours, the mixture was quenched by the addition of pH 6 phosphate buffer and partitioned between water and 3 portion of ethyl ether. The combined organic fractions were washed with water and brine, dried, filtered and concentrated. The residue was dissolved in 10 mL of 4N HCl/dioxane and stirred overnight. The mixture was diluted with ethyl ether and placed in a freezer for 3 days. The precipitate was collected, washed with ether and dried under vacuum to provide 1.17 g (74%) of the title compound. MS (DCI, NH<sub>3</sub>): 272 (MH)<sup>+</sup>; 289 (M+NH<sub>4</sub>)<sup>+</sup>.



Example 1130B

4-(N-Oxy-2-cyclohexyloxyacetaldoximinomethyl)-2-(2-methylphenyl)benzoic acid, methyl ester

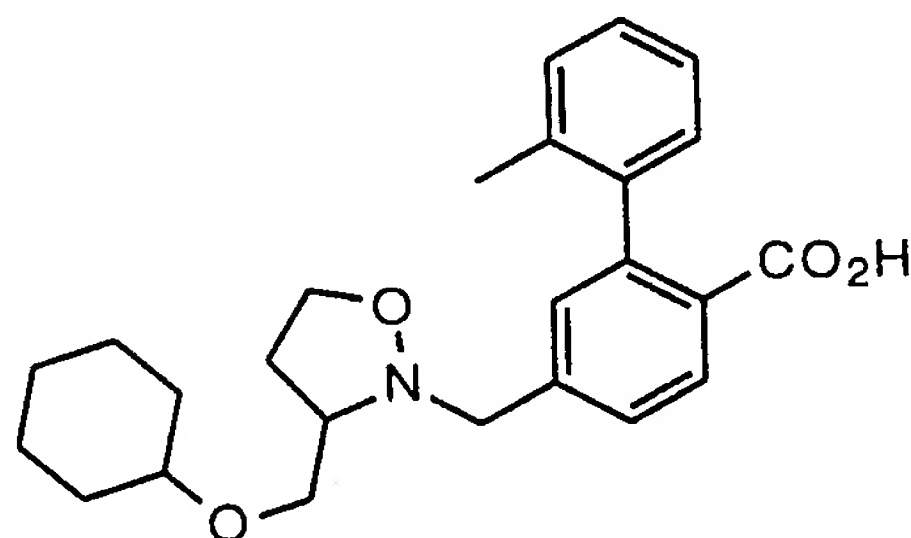
A solution of example 1130A (1.15 g, 4.29 mmol) and 2-cyclohexyloxyacetaldehyde (0.55 g, 3.90 mmol) in 10 mL of acetonitrile was treated with powdered, activated 4Å molecular sieves (0.50 g) and potassium hydrogen carbonate (0.47 g, 4.70 mmol) and stirred overnight. The mixture was filtered through a plug of silica gel (prewetted with ether) and the pad washed well with ether. The filtrate was concentrated to provide 0.82 g (55%) of the title compound. MS (DCI, NH<sub>3</sub>): 272 (MH)<sup>+</sup>.



Example 1130C

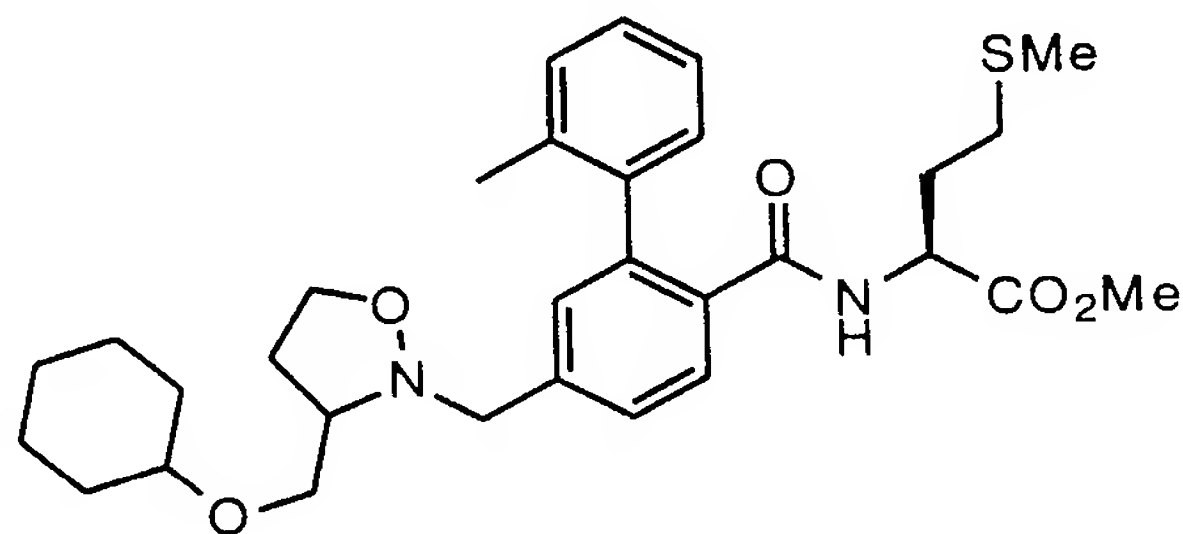
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoic acid methyl ester

A solution of example 1130B (0.81 g, 2.05 mmol) in 30 mL of chloroform was heated to 75°C under 640 psi of ethylene for 72 hours. The mixture was cooled to room temperature and vented. The chloroform was evaporated and the residue purified by column chromatography on silica gel (40 g, 15% ethyl acetate/hexanes) to provide 363 mg (40%) of the title compound. MS (ESI<sup>+</sup>): 424 (MH<sup>+</sup>).

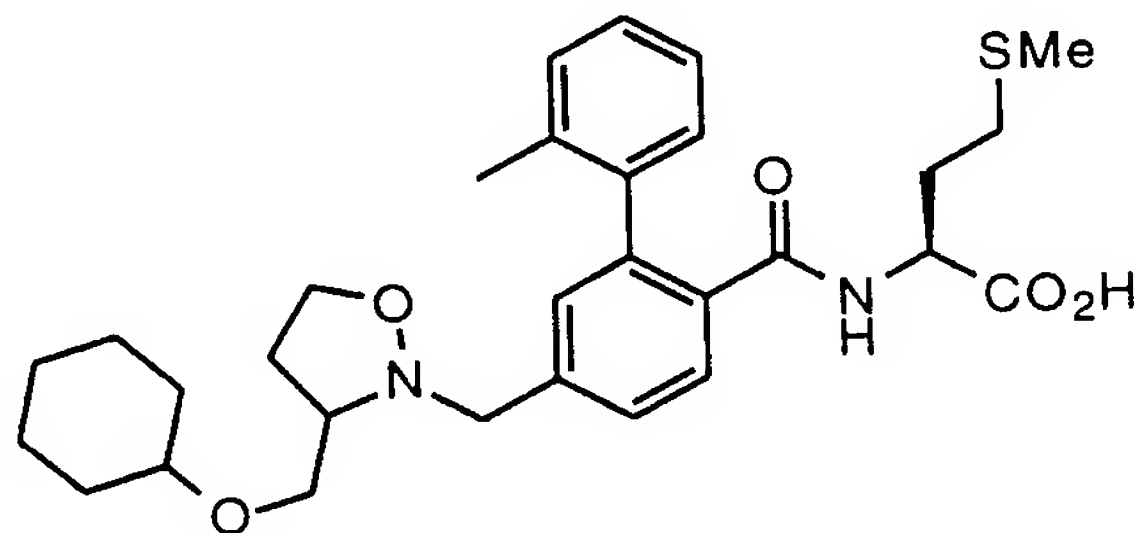


Example 1130DN-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoic acid

A mixture of example 1130C (355 mg, 0.84 mmol) and sodium hydroxide (1 mL of a 4N aqueous solution, 4 mmol) in 4 mL of ethanol was heated to reflux for 6 hours and then cooled to room temperature. The mixture was diluted with water and the pH adjusted to 5 with aqueous phosphoric acid. The mixture was extracted with 3 portions of ethyl acetate and the combined organic fractions were washed with water and brine, dried, filtered and concentrated to provide 270 mg (78%) of the title compound. MS (ESI<sup>+</sup>): 410 (MH<sup>+</sup>).

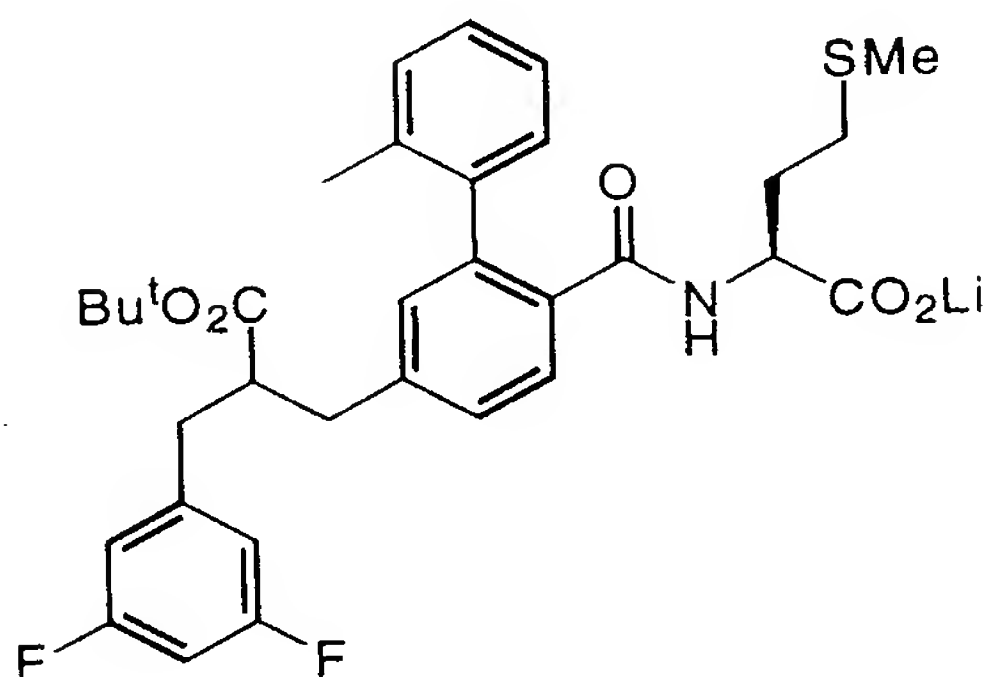
Example 1130EN-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1178I, example 1130D (265 mg, 0.65 mmol) provided 147 mg (41%) of the title compound. MS (ESI<sup>+</sup>): 555 (MH<sup>+</sup>); (ESI<sup>-</sup>): 553 (M-H).

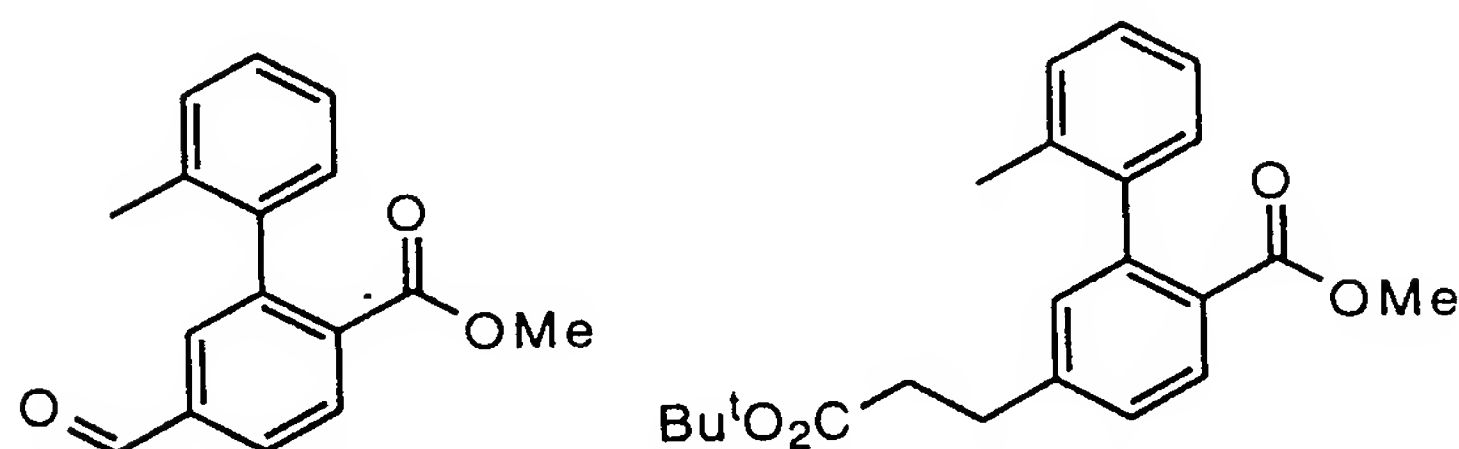
Example 1130FN-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104, example 1130E (140 mg, 0.25 mmol) provided 78 mg (70%) after preparative HPLC purification. <sup>1</sup>H nmr (300 MHz, CDCl<sub>3</sub>): δ 7.91, m, 1H; 7.56, m, 1H; 7.13 - 7.35, m, 5H; 5.99, d, 1H; 4.62, m, 2H; 4.41, m, 1H; 4.24, m, 1H; 4.05, m, 1H; 3.91, m, 1H; 3.52, m, 1H; 3.33, m, 1H; 2.40, m, 1H; 2.29, m, 1H; 2.00 - 2.28, m, 7H; 2.02, s, 3H; 1.89, bm, 3H; envelope, 1.43 - 1.75, 5H; 1.26, bm, 5H.

MS (ESI+): 541 (MH+); (ESI-): 539 (M-H). Calc'd for  $C_{30}H_{40}N_2O_5S \cdot 1.10$  TFA; C 58.06; H 6.22; N 4.21; Found: C 57.97; H 6.28; N 4.17



Example 1135



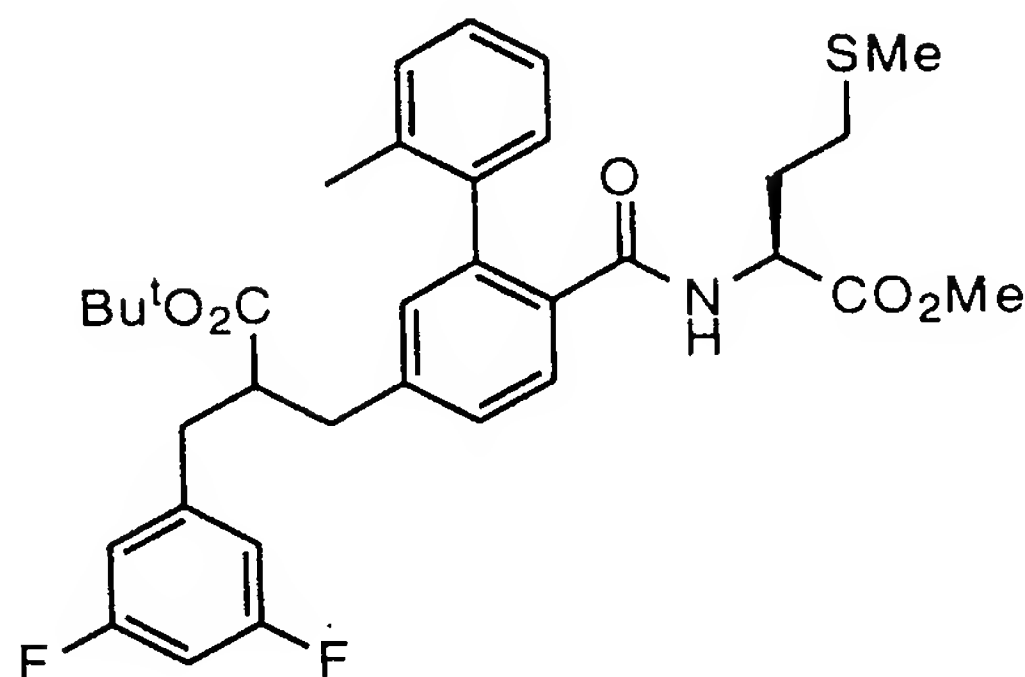
Example 1135A

Methyl 4-(tert-Butoxycarbonyl)ethyl-2-(2-methylphenyl)benzoate

To a solution of (t-butoxycarbonylmethyl)triphenylphosphonium bromide (10.98 g, 24.0 mmol) in THF (150 mL) at 0 °C was added potassium t-butoxide (1.0 M in THF, 24 mL) over 5 min. After 2 h, the aldehyde in THF (10 mL) was added slowly over 5 min., and the reaction was further stirred for 30 min. The reaction mixture was diluted with hexane (200 mL), and the resulting muddy mixture was filtered through silica gel (200 g), rinsed with ether, and concentrated to give an intermediate olefin.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (d, 1 H), 7.59 (d, 1 H), 7.54 (dd, 1 H), 7.37 (d, 1 H), 7.30-7.27 (m, 3 H), 7.06 (d, 1 H), 6.44 (d, 1 H), 3.61 (s, 3 H), 2.06 (s, 3 H), 1.52 (s, 9 H). MS(CI/ $\text{NH}_3$ ) m/z: 353 ( $\text{M}+\text{H}$ ) $^+$ , 370 ( $\text{M}+\text{NH}_4$ ) $^+$ .

That intermediate was mixed with palladium on carbon (10%, 2.0 g) in ethanol (30 mL), and was stirred under a hydrogen balloon overnight. The mixture was then filtered through Celite<sup>TM</sup> (5 g), and the filtrate was concentrated. The residue was then redissolved in ether (100 mL) and the solution was filtered through silica gel (30 g). Concentration of the filtrate afforded the title compound (7.27 g, 99% for 2 steps).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )

8700  $\delta$  7.91 (d, 1H), 7.28-7.15 (m, 4 H), 7.07-7.03 (m, 2 H), 3.60 (s, 3 H), 2.97 (t, 2 H), 2.57 (t, 2 H), 2.05 (s, 3 H), 1.40 (s, 9 H). MS(CI/NH<sub>3</sub>) m/z: 355 (M+H)<sup>+</sup>, 372 (M+NH<sub>4</sub>)<sup>+</sup>.



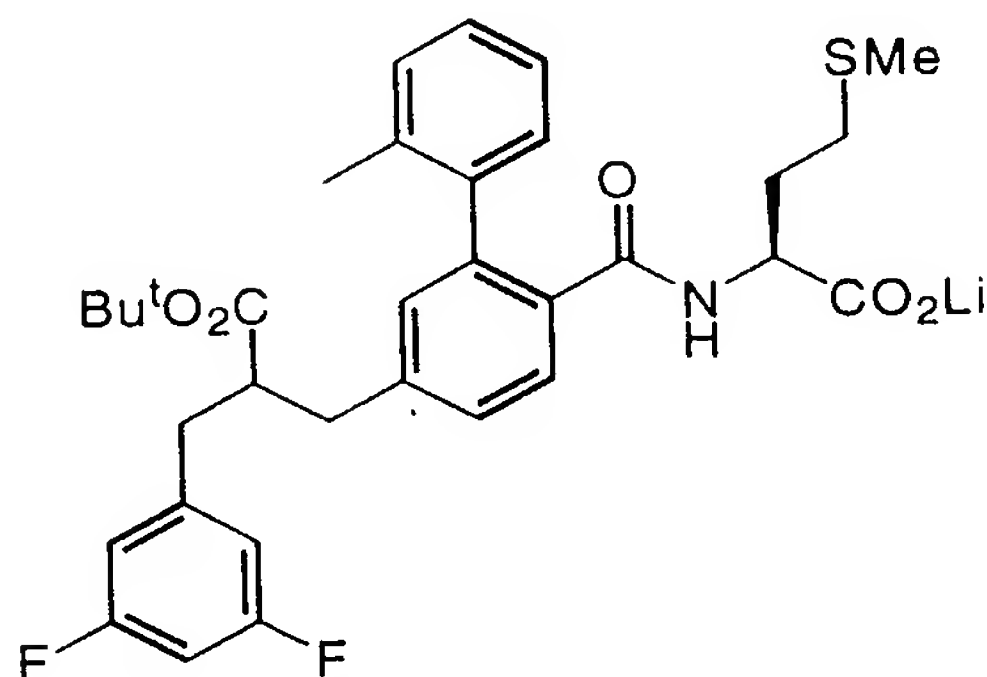
Example 1135B

8705 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

To a -78 °C solution of intermediate 1135A (487 mg, 1.32 mmol) in THF (5 mL) was added sodium hexamethyldisilylazide (NaHMDS, 1.0 M in THF, 1.6 mL). After 30 min., 3,5-difluorobenzyl bromide (329 mg, 1.59 mmol) was added to the reaction, and the reaction mixture was then gradually warmed to room temperature over 2 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 8% ethyl acetate in hexane (the product and starting material had identical R<sub>f</sub> on TLC) in to give the methyl ester intermediate.

The product obtained from the previous step was stirred with saturated aqueous LiOH (2 mL) in MeOH (3 mL) at 50 °C overnight. Then, the reaction mixture was carefully adjusted to pH 3 to 4, and extracted with ethyl acetate (100 mL). The organic layer was rinsed once with brine (15 mL), and dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude monoacid obtained this way was stirred with *L*-methionine methyl ester hydrochloride (383 mg, 2 mmol), 1-hydroxybenzotriazole (266 mg, 2.0 mmol), triethylamine (303 mg, 3.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (400 mg, 2.0 mmol) in DMF for 5 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (2 X 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 20% ethyl acetate in hexane to give the title compound (277 mg, 34% for 3 steps). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.92 (2 d's, 1 H), 7.37-7.12 (m, 5 H), 7.02 (d, 1 H), 6.75-6.60 (m, 3 H), 5.90 (br d, 1 H), 4.62 (m, 1

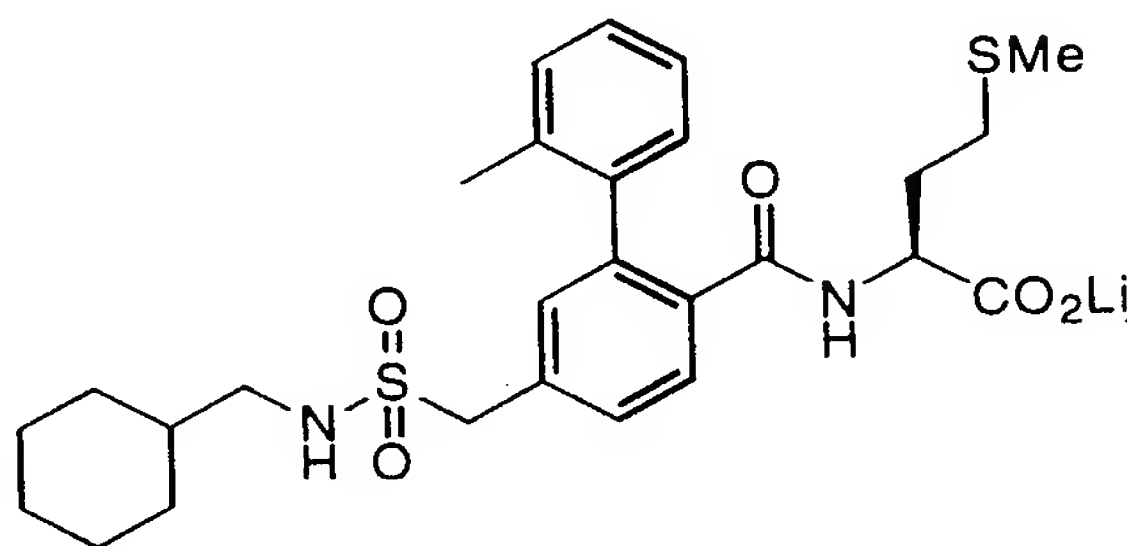
8730 H), 3.66 (s, 3H), 3.05-2.72 (m, 5 H), 2.17, 2.06, 2.02, 2.00 (4 s's, 6 H), 2.03 (m, 2 H),  
1.95 (m, 1 H), 1.60 (m, 1 H), 1.22 (3 s's, 9 H). MS(CI/NH<sub>3</sub>) m/z: 612 (M+H)<sup>+</sup>.



Example 1135C

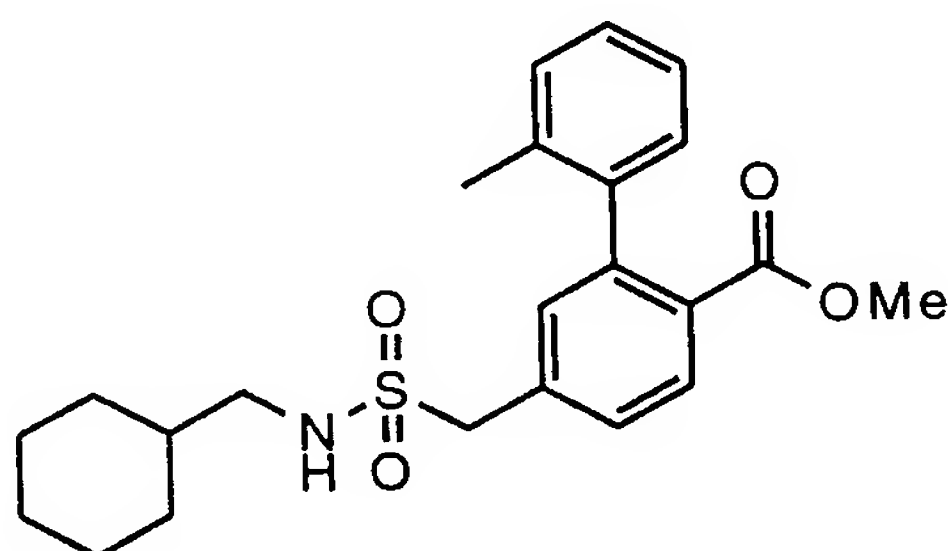
8735 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the intermediate 1135B (66 mg) to the title lithium salt (65 mg, 100%). <sup>1</sup>H NMR (300 MHz, MeOD-d<sub>4</sub>) δ 7.52 (br s, 1 H), 7.35-7.21 (m, 5 H), 7.06 (m, 1 H), 6.87-6.72 (m, 3 H), 4.24 (m, 1 H), 3.00-2.85 (m, 5 H), 2.08-1.93 (m, 8 H), 1.84 (m, 1 H), 1.65 (m, 1 H),  
8740 1.18-1.12 (3 s's, 9 H). MS(ESI<sup>-</sup>) m/z: 596 (M-H)<sup>-</sup>.



Example 1138

8745



Example 1138A



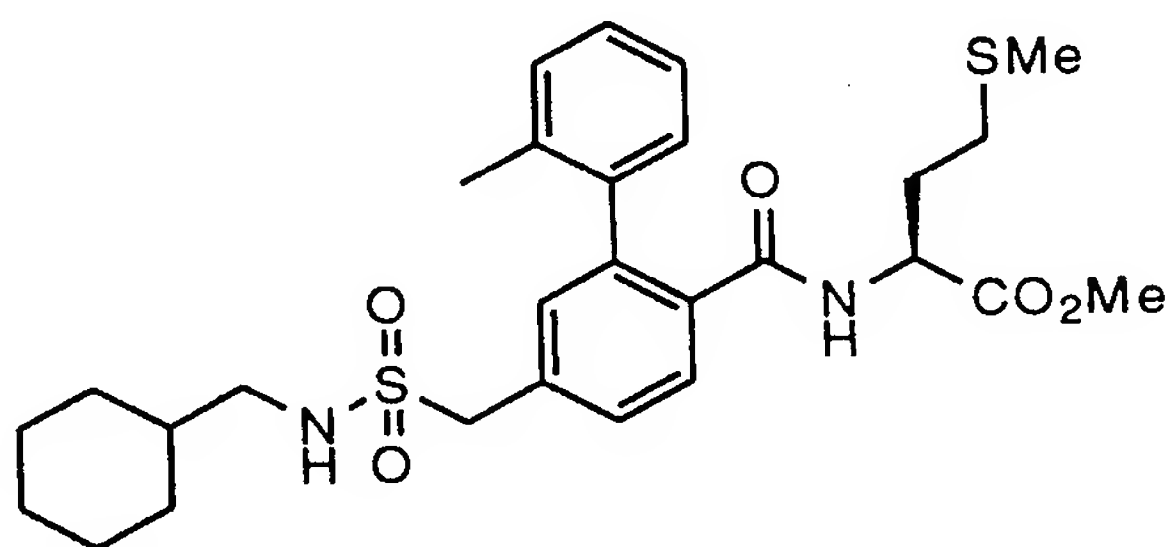
Methyl 4-(*N*-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoate

8750 To a room temperature solution of 1178D (1.21 g, 3.79 mmol) in THF (10 mL) was added potassium thioacetate (0.48 g, 4.2 mmol). After 5 hours, NaOH (3.5 M in water, 3 mL) was added, and the reaction mixture was stirred another 30 min. Reaction mixture was then acidified with HCl (1.0 M, 15 mL), and partitioned between ethyl acetate (100 mL) and water (10 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated.

8755 The residue desolved acetic acid (5 mL) and hydrogen peroxide (30%, 5 mL), and heated at 80 °C for 16 hours. The reaction mixture was diluted with brine (10 mL), and extrated with ethyl acetate (3 X 30 mL). The combined extrats were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the crude sulfonic acid. MS(ESI-) m/z: 319 (M-H)<sup>-</sup>.

8760 The crude sulfonic acid was then refluxed with thionyl chloride (5 mL) and DMF (0.5 mL) for 8 hours. Solvent was then evaporated, and the residue was dried under high vacuum (5 mmHg) for 3 hours. The sulfonyl chloride obtained this way was then desolved in DCM (10 mL), and to it was added cyclohexylmethylamine (0.5 g) and triethylamine (2 mL). Afte 20 min., the reaction was diluted with ether (20 mL), filtered through silica gel  
8765 (20 g), rinsed with ether (50 mL), and concentrated. The residue was purified by column chromatography with hexane:chloroform:ethyl acetate (50:50:10) to give the title compound (61 mg, 3.9%, 3 steps). 7.97 (d, 1 H), 7.46 (dd, 1 H), 7.30-7.15 (m, 5 H), 7.05 (br d, 1 H), 4.30 (s, 2 H), 3.61 (s, 3 H), 2.83 (t, 2 H), 2.07 (s, 3 H), 1.80-0.90 (m, 11 H).MS(CI/NH<sub>3</sub>) m/z: 433 (M+NH<sub>4</sub>)<sup>+</sup>.

8770



Example 1138B

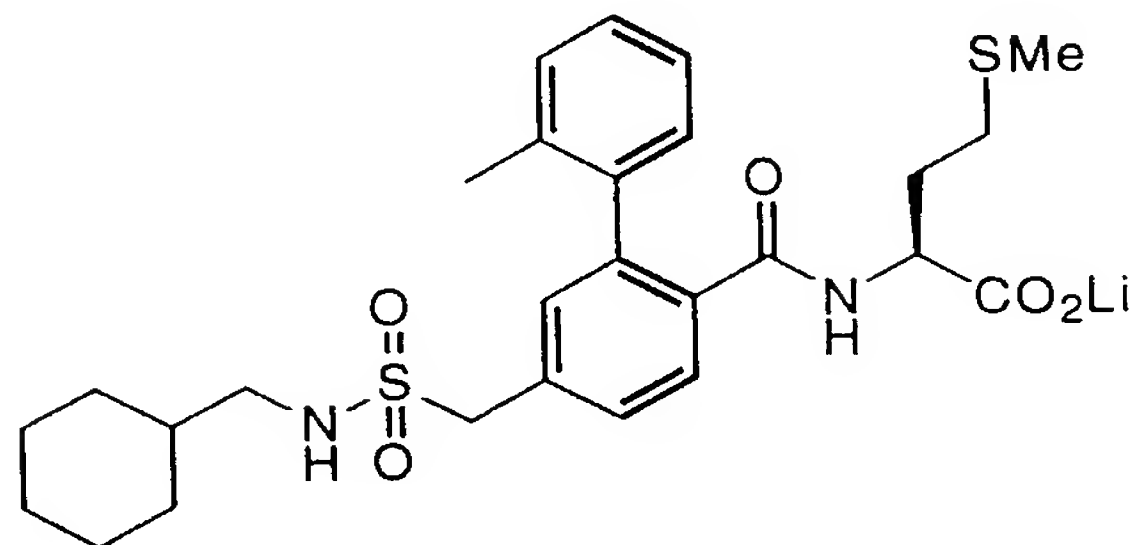
*N*-[4-(*N*-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8775

Methyl Ester

The procedures described in the Example 403E and 403F were used here to convert the above intermediate 1138A (45 mg) to the title methyl ester (37 mg, 63%). <sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>) δ 7.97 (2 d'd, 1 H), 7.48 (d, 1 H), 7.37-7.22 (m, 5 H), 5.93 (d, 1 H), 4.63

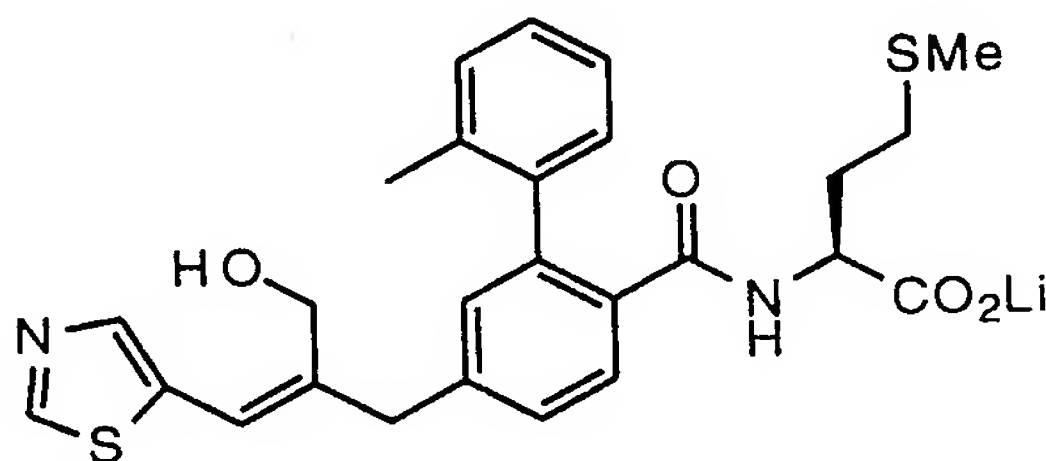
(m, 1 H), 4.29 (s, 2 H), 3.67 (s, 3 H), 2.87 (t, 2 H), 2.20-2.00 (m, 8 H), 2.86 (m, 1 H),  
 8780 2.80-0.80 (m, 12 H). MS(ESI-) m/z: 545 (M-H)<sup>-</sup>.



### Example 1138C

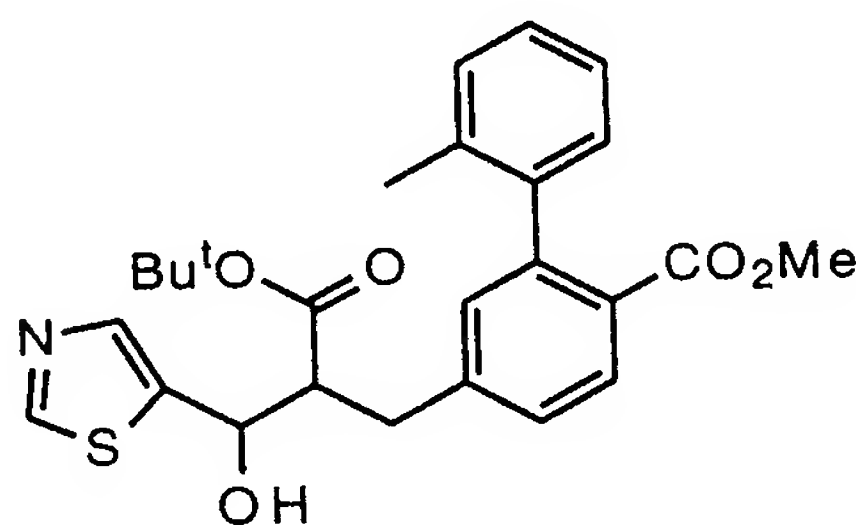
N-[4-(N-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine  
 8785 Lithium Salt

The procedure described in the Example 403I was used here to convert the  
 intermediate 1135B (32 mg) to the title lithium salt (32 mg, 100%). <sup>1</sup>H NMR (300 MHz,  
 dmso-d<sub>6</sub>) δ 7.46 (d, 1 H), 7.36 (m, 1 H), 7.20-6.92 (m, 6 H), 7.08 (m, 1 H), 4.30 (s, 2  
 H), 3.58 (m, 1 H), 2.64 (br d, 2 H), 2.00-1.80 (m, 8 H), 1.80-0.68 (m, 13 H). MS(ESI-)  
 8790 m/z: 531 (M-H)<sup>-</sup>.



### Example 1162

8795

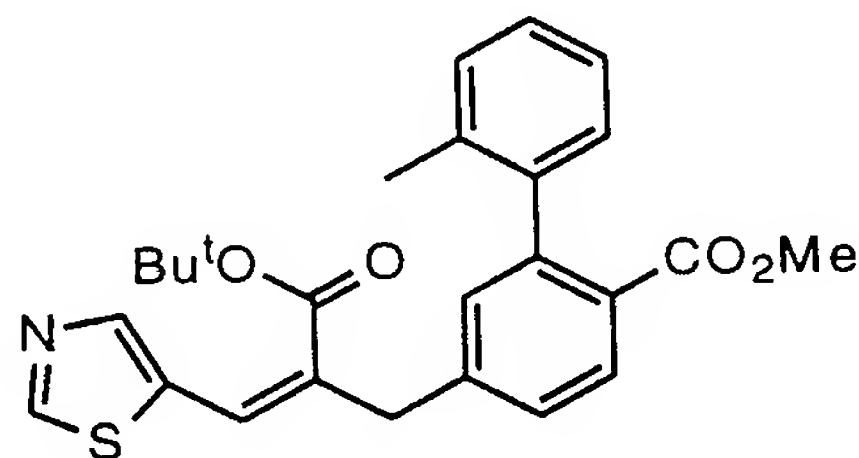


### Example 1162A

Methyl 4-[2-t-Butoxycarbonyl-3-hydroxy-3-(thiazol-5-yl)propyl]-2-(2-  
methylphenyl)benzoate

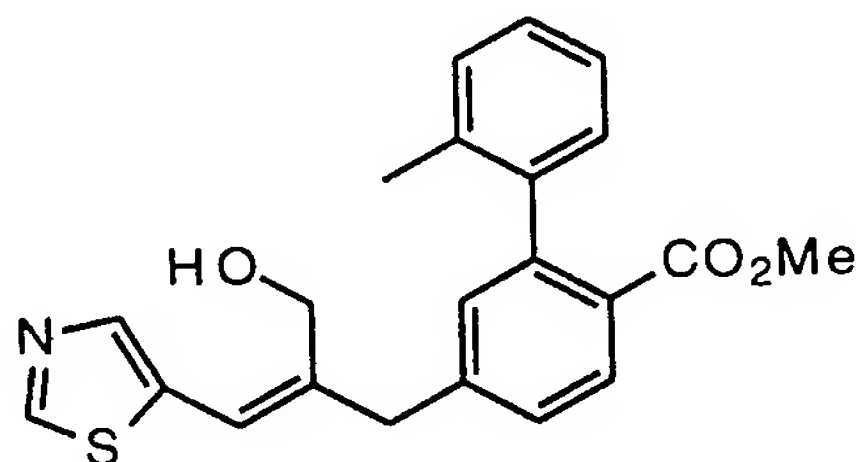


8800 To a -78 °C solution of intermediate 1135A (1.75 g, 4.94 mmol) in THF (20 mL) was added sodium hexamethyldisilylazide (1.0 M in THF, 5.9 mL). After 10 min, 5-thiazolcarboxaldehyde (838 mg, 7.41 mmol) in THF (10 mL) was added to the reaction, and the reaction mixture was then gradually warmed to room temperature over 2 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL).  
 8805 The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 50% ethyl acetate in hexane to give the title intermediate as a mixture of diastereomers (1.41 g, 61%, ratio of diastereomers, 2.5:1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.90 (2 br s's, 1 H), 7.91 (2 d's, 1 H), 7.80 (2 br s's, 1 H), 7.31-7.25 (m, 5 H), 7.05 (m, 2 H), 5.30, 5.05 (2 m'm, 1 H), 3.60 (s, 3 H), 3.14-3.00 (m, 3 H), 2.05 (4 s's, 3 H), 1.26, 1.19, 1.18 (3 s's, 9 H). MS(CI/NH<sub>3</sub>) m/z: 468 (M+H)<sup>+</sup>.  
 8810



#### Example 1162B

8815 Methyl 4-[E-2-t-Butoxycarbonyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoate  
 To a solution of intermediate 1162A (267 mg, 0.57 mmol) in 1,2-dichloroethane (10 mL) was added pyridine (0.5 mL), POCl<sub>3</sub> (0.2 mL) and DBU (5 drops) in that order. After 4 hours at room temperature, the reaction mixture was diluted with ether (10 mL), filtered through silica gel (30 g), rinsed with ether (2 X 20 mL), and concentrated. The residue  
 8820 was purified by column chromatography with 30% ethyl acetate in hexane to give the title compound as a single isomer (230 mg, 90%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.81 (s, 1 H), 8.02 (s, 1 H), 7.96 (s, 1 H), 7.89 (d, 1 H), 7.26-7.15 (m, 5 H), 7.02 (m, 2 H), 4.06 (br s, 2 H), 3.59 (s, 3 H), 2.00 (s, 3 H), 1.43 (s, 9 H). MS(CI/NH<sub>3</sub>) m/z: 450 (M+H)<sup>+</sup>.

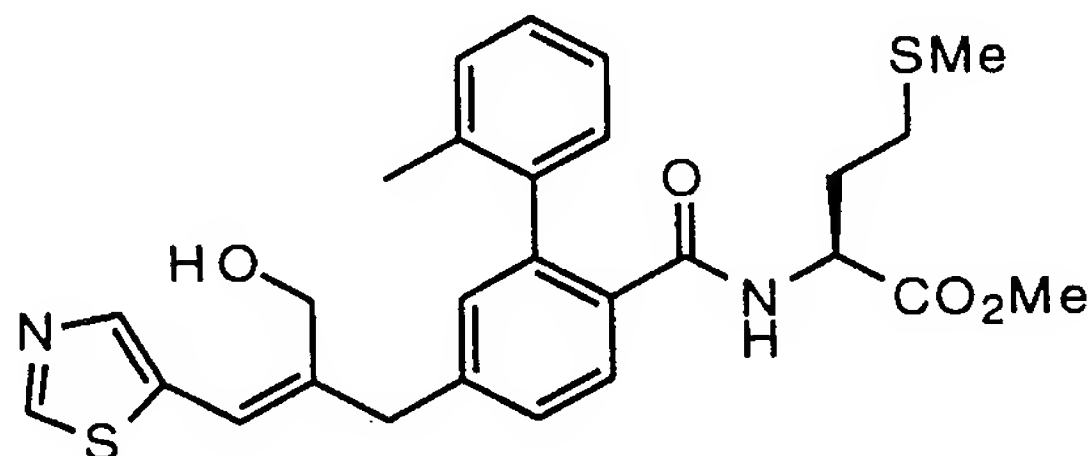


#### Example 1162C

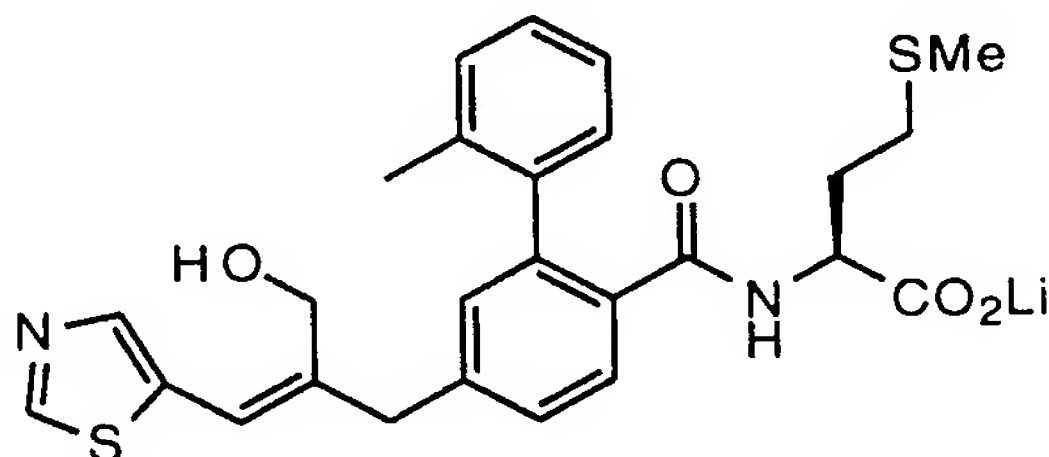
8825

Methyl 4-[E-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoate

A mixture of intermediate 1162B (205 mg, 0.456 mmol) and HCl (anhydrous, 4.0 M in 1,4-dioxane, 2 mL) was stirred for 16 h at room temperature. The reaction mixture was then concentrated to dryness, and the residue was desolved in THF (3 mL) and cooled to 0 °C. To it was added isobutyl chloroformate (0.089 mL, 0.685 mmol) and *N*-methylmorpholine (0.15 mL, 1.4 mmol). After 15 min. at 0 °C, sodium borohydride (53 mg, 1.4 mmol) was added to the reaction, followed by addition of methanol (1 mL). The reaction was then stirred at room temperature for 2 hours. The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 50% ethyl acetate in hexane to give the title compound (69.7 mg, 40%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.70 (s, 1 H), 7.90 (d, 1 H), 7.81 (s, 1 H), 7.27-7.15 (m, 4 H), 7.05 (m, 2 H), 6.93 (s, 1 H), 4.21 (d, 2 H), 3.85 (s, 2 H), 3.59 (s, 3 H), 2.02 (s, 3 H). MS(CI/NH<sub>3</sub>) m/z: 380 (M+H)<sup>+</sup>.

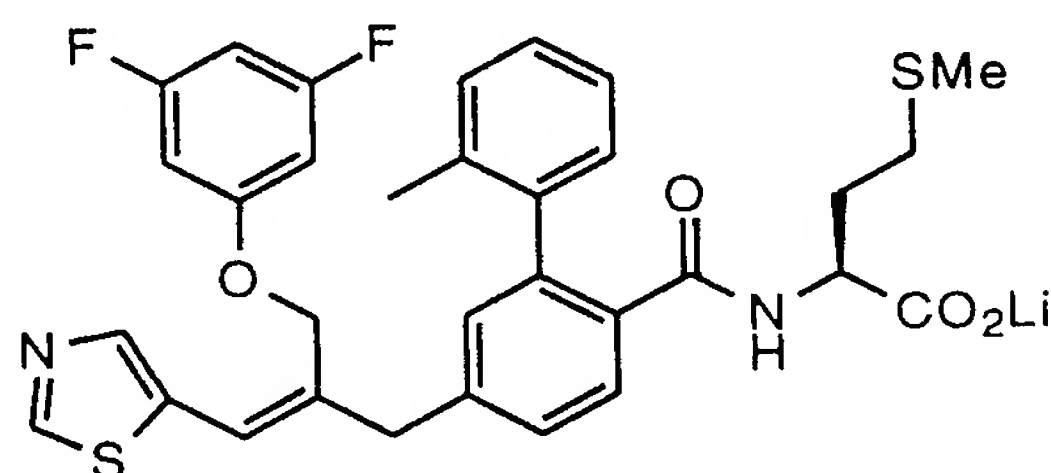
Example 1162 DN-{4-[E-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine Methyl Ester

The procedures described in the Example 403E and 403F were used here to convert the intermediate 1162D (69 mg) to the title methyl ester (74 mg, 80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.78 (s, 1 H), 7.95-7.81 (m, 2 H), 7.35-7.15 (m, 5 H), 7.01 (s, 1 H), 6.94 (s, 1 H), 5.86 (m, 1 H), 4.62 (m, 1 H), 4.22 (s, 2 H), 3.84 (s, 2 H), 3.77 (s, 3 H), 2.14-2.00 (m, 8 H), 1.87 (m, 1 H), 1.60 (m, 1 H). MS(CI/NH<sub>3</sub>) m/z: 511 (M+H)<sup>+</sup>.

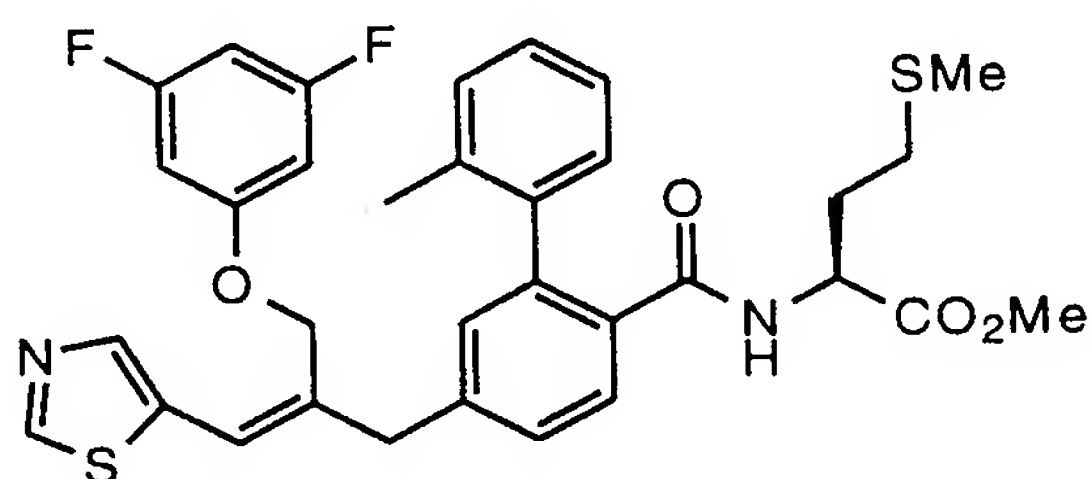
Example 1162 E

*N*-{4-[*E*-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the intermediate 1162D (20.2 mg) to the title lithium salt (20 mg, 100%). <sup>1</sup>H NMR (300 MHz, dmso-d<sub>6</sub>) δ 8.97 (s, 1 H), 7.90 (s, 1 H), 7.47 (d, 1 H), 7.25 (dd, 1 H), 7.22-7.07 (m, 4 H), 6.92 (m, 2 H), 6.89 (m, 1 H), 5.42 (t, 1 H), 3.99 (d, 2 H), 3.75 (s, 2 H), 3.60 (m, 1 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.90 (br s, 6 H), 1.68 (m, 1 H), 1.55 (m, 1 H). MS(ESI-) m/z: 495 (M-H)<sup>-</sup>.



Example 1163

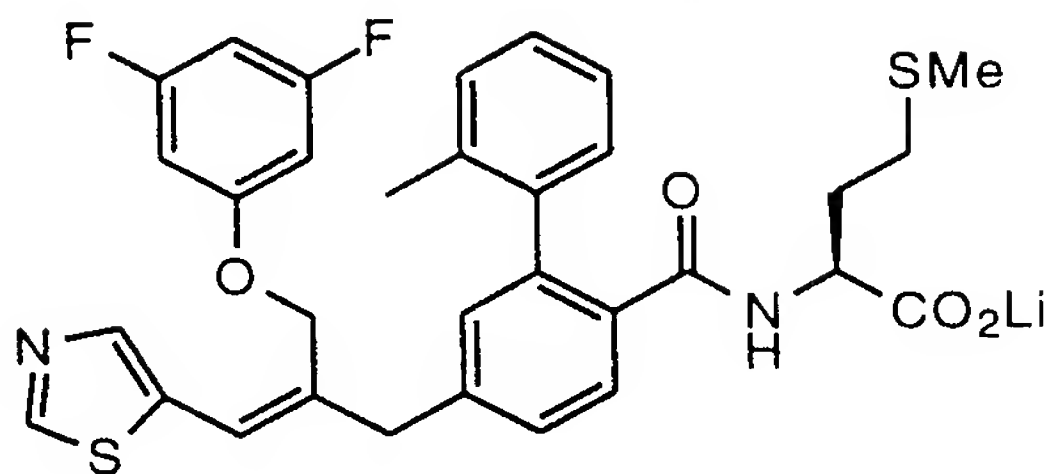


Example 1163A

*N*-{4-[*E*-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine Lithium Salt

To a 0 °C solution of triphenylphosphine (55 mg, 0.21 mmol) in DCM (1 mL) was added diethyl azodicarboxylate (36 mg, 0.21 mmol). After 10 min., the solution thus prepared was transferred to a 0 °C solution of intermediate 1162D (35.1 mg, 0.069 mmol) and 3,5-difluorophenol (27.3 mg, 0.21 mmol) in DCM (1 mL). After the reaction mixture was stirred at room temperature for 15 hours, it was diluted with ether (5 mL), filtered through silica gel (5 g), rinsed with ether (10 mL), and concentrated. The residue was purified twice by column chromatography with 30% ethyl acetate in hexane to give the title methyl ester (13.2 mg, 31%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.78 (s, 1 H), 7.95-7.85 (m, 2 H), 7.35-7.05 (m, 9 H), 7.02 (s, 1 H), 6.97 (s, 1 H), 5.88 (m, 1 H), 4.62 (m, 1 H),

4.49 (s, 2 H), 3.92 (s, 2 H), 3.66 (s, 3 H), 2.17-1.98 (m, 8 H), 1.87 (m, 1 H), 1.60 (m, 1 H). MS(CI/NH<sub>3</sub>) m/z: 623 (M+H)<sup>+</sup>.



8885

Example 1163B

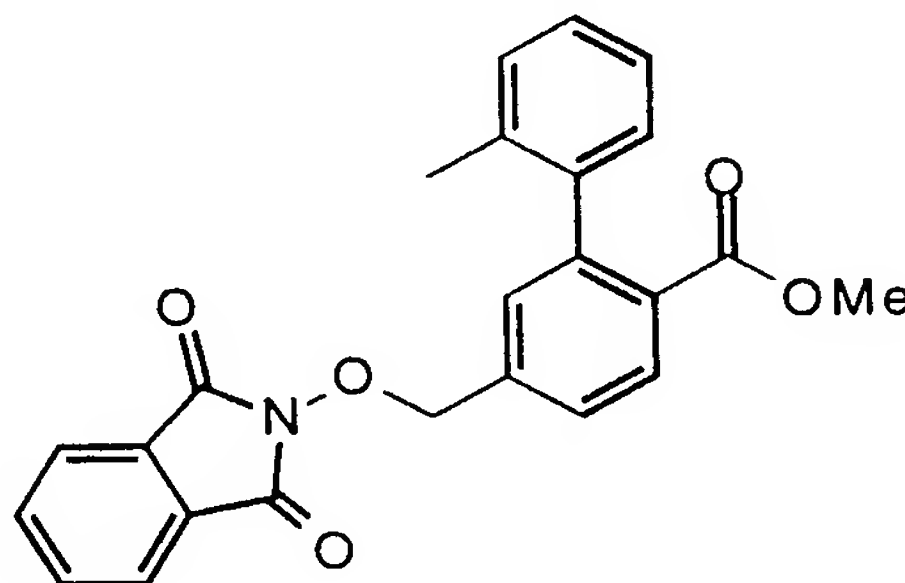
N-{4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the  
 8890 intermediate 1163A (13.2 mg) to the title lithium salt (13.0 mg, 100%). <sup>1</sup>H NMR (300 MHz, dmso-d<sub>6</sub>) δ 9.05 (s, 1 H), 7.98 (s, 1 H), 7.47 (d, 1 H), 7.25 (dd, 1 H), 7.22-7.07 (m, 5 H), 6.95 (m, 1 H), 6.87 (m, 1 H), 6.80-6.70 (m, 4 H), 4.62 (s, 2 H), 3.87 (s, 2 H), 3.60 (m, 1 H), 2.10-1.92 (m, 2 H), 1.90 (br s, 6 H), 1.68 (m, 1 H), 1.55 (m, 1 H). MS(ESI<sup>-</sup>) m/z: 607 (M-H)<sup>-</sup>.

8895

Example 1176

8900

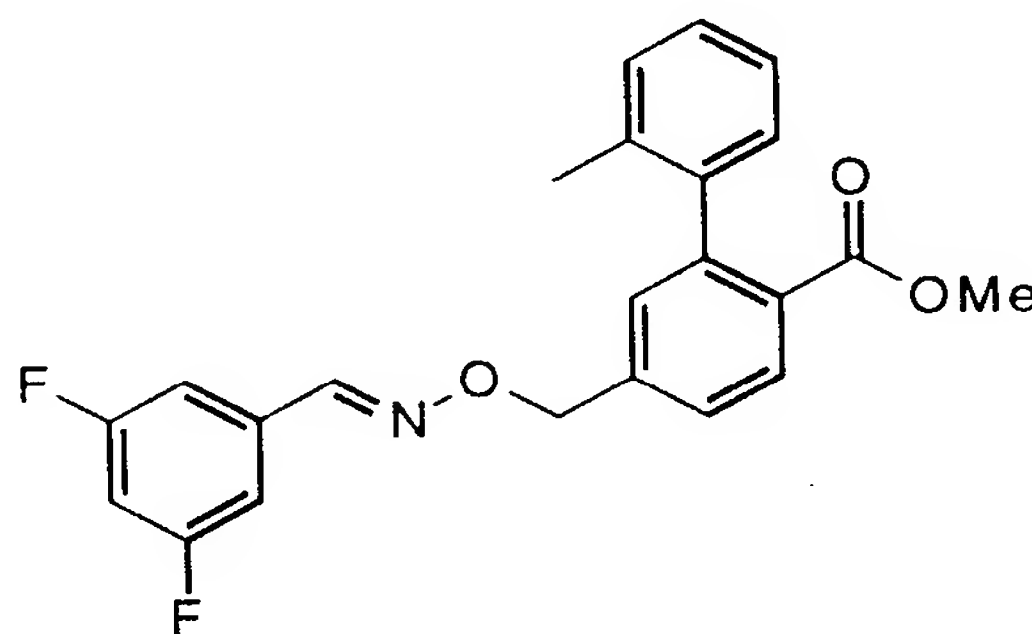


Example 1176A

4-Phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

To a stirred solution at 0°C under N<sub>2</sub> of 4-hydroxymethyl-2-(2-  
 8905 methylphenyl)benzoic acid methyl ester (5.00 g, 19.5 mmol), prepared as in Example 1178A-C, N-hydroxyphthalimide (3.19 g, 19.5 mmol), and triphenylphosphine (5.12 g,

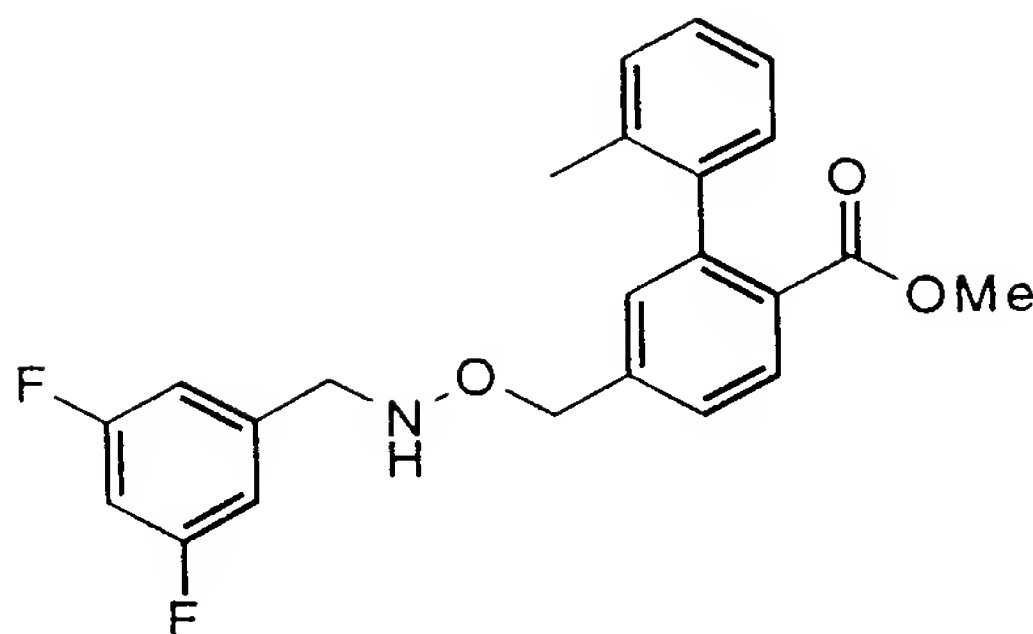
19.5 mmol) in anhydrous THF (150 mL) was added diethyl azodicarboxylate (3.38 mL, 21.5 mmol). Cooling bath removed and reaction warmed to 50°C overnight. Solvents concentrated *in vacuo*, and residue taken up in ether and washed with 2M Na<sub>2</sub>CO<sub>3</sub> (3x), water, and brine. Organic layer dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 20% EtOAc/Hexanes to afford the desired product as a white solid (3.32 g, 41%). <sup>1</sup>H (300MHz, CDCl<sub>3</sub>, δ) 7.99 (1H, d, J=8Hz), 7.79 (4H, m), 7.63 (1H, dd, J=7&2Hz), 7.38 (1H, d, J=2Hz), 7.30-7.10 (3H, m), 7.02 (1H, dd, J=8&2Hz), 5.26 (2H, s), 3.62 (3H, s), 1.99 (3H, s).



#### Example 1176B

#### 4-(N-(3,5-difluorobenzylidenoyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

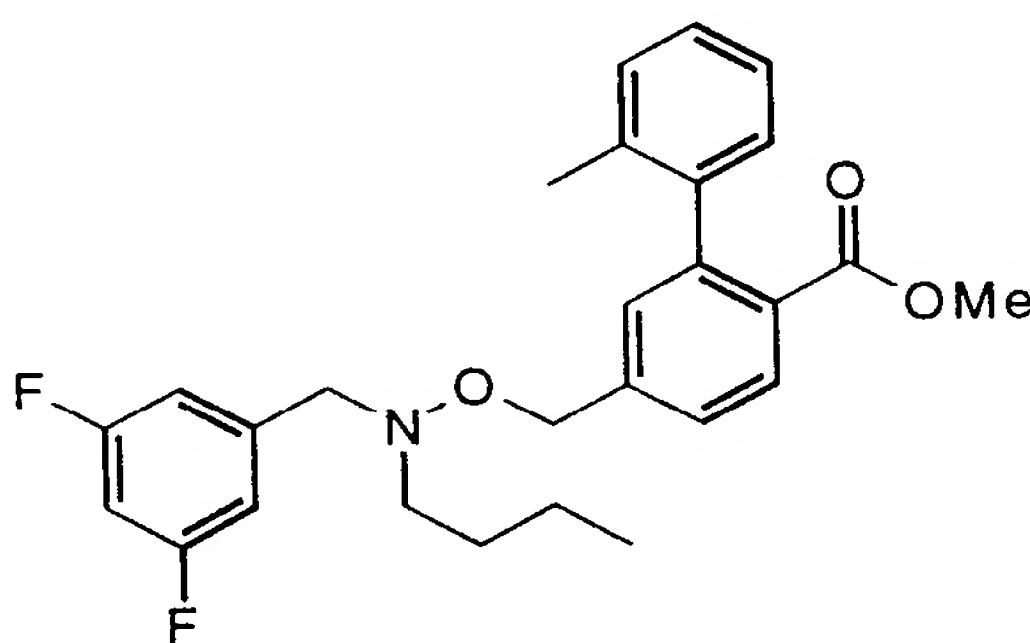
To a solution under N<sub>2</sub> of 4-phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (575 mg, 1.43 mmol), prepared as in Example 1176A, in boiling EtOH (10 mL) was added while hot 55% hydrazine hydrate (0.089 mL, 1.58 mmol). Reaction allowed to cool to ambient temperature, and to this mixture was added 3,5-difluorobenzaldehyde (0.172 mL, 1.58 mmol). Reaction stirred overnight at ambient temperature. Solvents concentrated *in vacuo*, and residue stirred with CCl<sub>4</sub> (30 mL) and MgSO<sub>4</sub> for 15 minutes at ambient temperature. Mixture filtered through celite, and filtrate concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 10% EtOAc/Hexanes to afford the desired product as a pale yellow solid (551 mg, 97%). m/e (ESI) 396 (MH<sup>+</sup>)

Example 1176C4-(N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

8935 To a stirred solution at room temperature under N<sub>2</sub> of 4-(N-(3,5-difluorobenzylidenoyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester (551 mg, 1.40 mmol), prepared as in Example 1176B, in MeOH (5 mL) was added sodium cyanoborohydride (263 mg, 4.18 mmol) and bromocresol green indicator. To this was

8940 less than 3). After reaction mixture remained yellow, it was allowed to stir 30 minutes at room temperature. Reaction quenched with 1.0M NaHCO<sub>3</sub>, and product extracted out with EtOAc (2x). Extracts washed with 1.0M NaHCO<sub>3</sub> (2x) and brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 25% EtOAc/Hexanes to afford the desired product. (254 mg, 46%). m/e

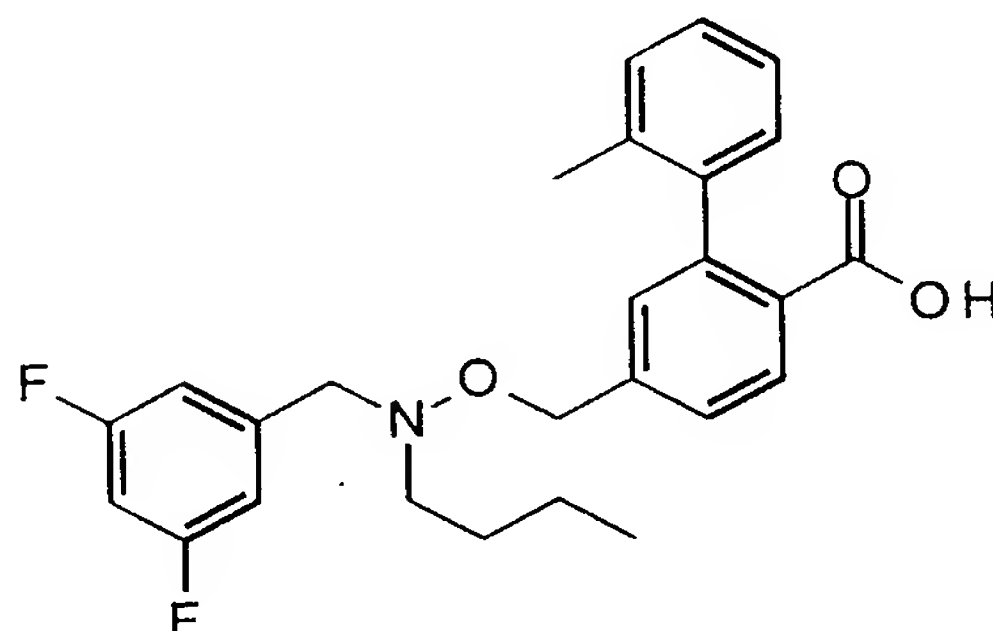
8945 (ESI) 398 (MH<sup>+</sup>)

Example 1176D4-(N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

8950

To a stirred solution at ambient temperature under N<sub>2</sub> of 4-(N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester (254 mg, 0.640 mmol), prepared as in Example 1176 C, in DMF (2 mL) was added potassium carbonate (265 mg, 1.92 mmol) and 1-iodobutane (0.146 mL, 1.28 mmol). Reaction stirred

8955 vigorously at 80°C overnight. Reaction diluted with EtOAc and washed with water and brine. Organic layer dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 7% EtOAc/Hexanes to 30% EtOAc/Hexanes to afford the desired product. (44 mg, 15%). m/e (ESI) 454 (MH<sup>+</sup>)

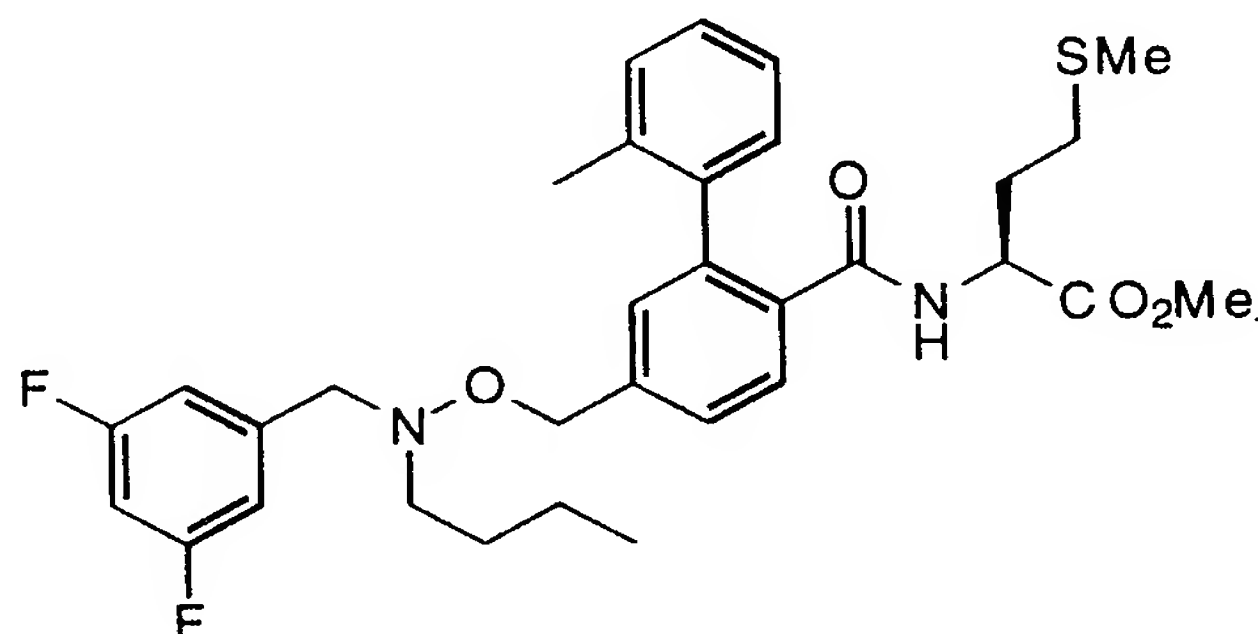


8960

Example 1176E4-(N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid

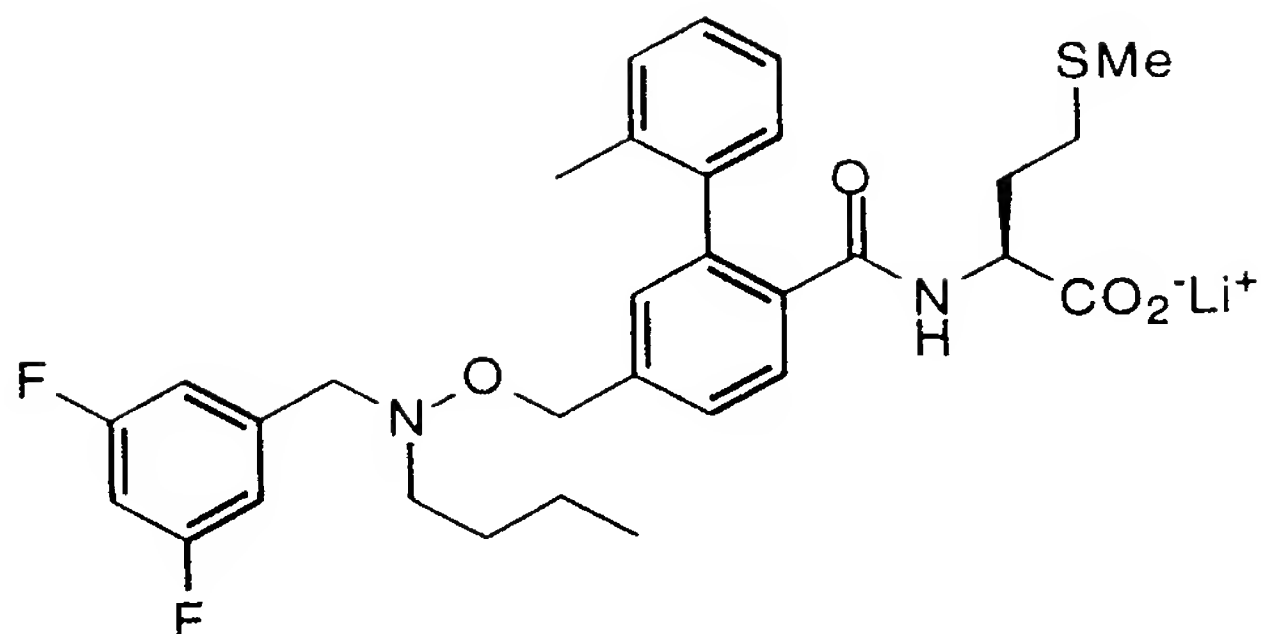
The desired acid was prepared using the method described in Example 403E starting with the compound prepared in Example 1176D.

8965

Example 1176FN-[4-N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

8970 The desired product was prepared using the method described in Example 403F starting with the compound prepared in Example 1176E.



Example 1176G

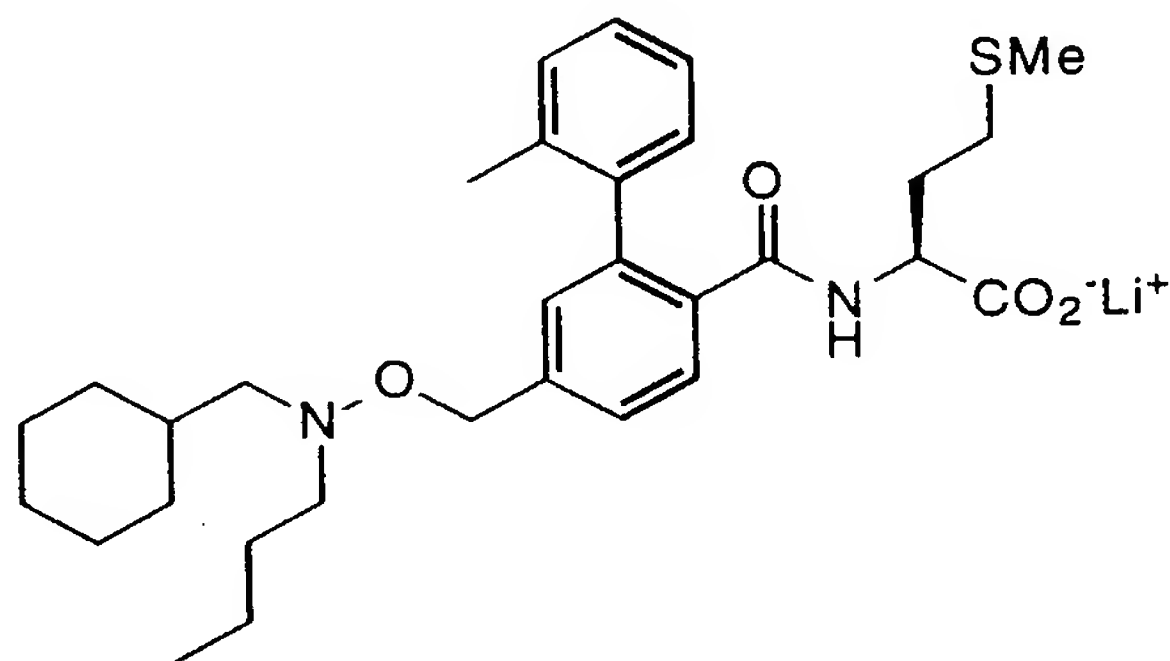
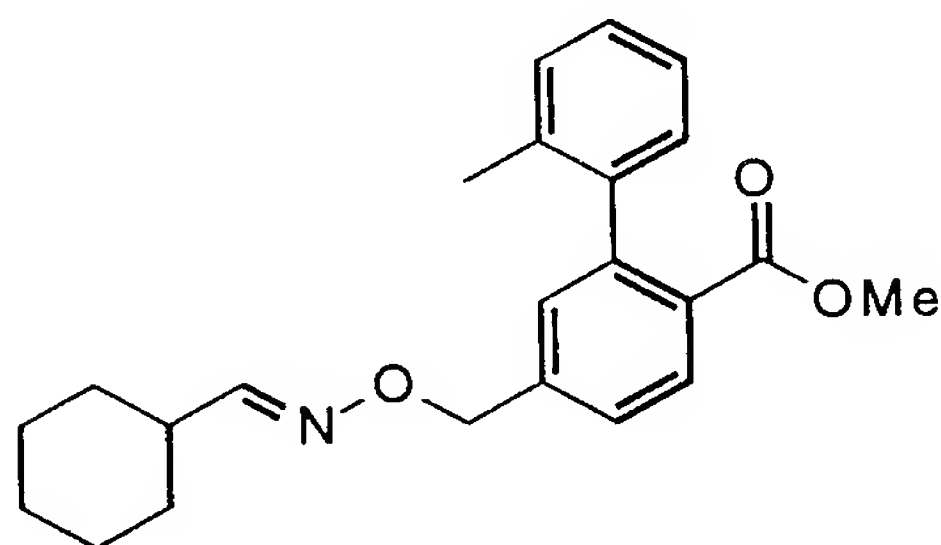
8975

N-[4-N--Butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-  
methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1176F. <sup>1</sup>H (300MHz, CDCl<sub>3</sub>, δ) 7.70 (1H, m), 7.30-7.00 (6H, m), 6.94 (1H, m), 6.85 (1H, dd, J=7&2Hz), 6.65 (1H, m), 4.53 (2H, bs), 4.03 (1H, m), 3.80 (2H, bs), 2.72 (2H, t, J=8Hz), 2.30-1.90 (5H, m), 1.80 (3H, s), 1.58 (2H, m), 1.50-1.20 (4H, m), 0.87 (3H, t, J=8Hz). m/e (ESI) 569 (MH<sup>-</sup>)

8980

8985

Example 1186Example 1186A

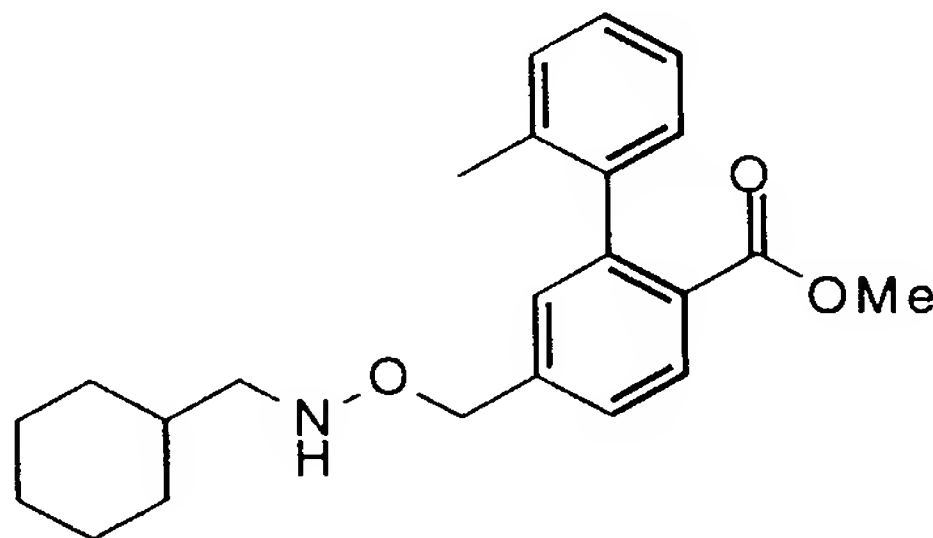
8990



4-N-(Cyclohexylmethylidene)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

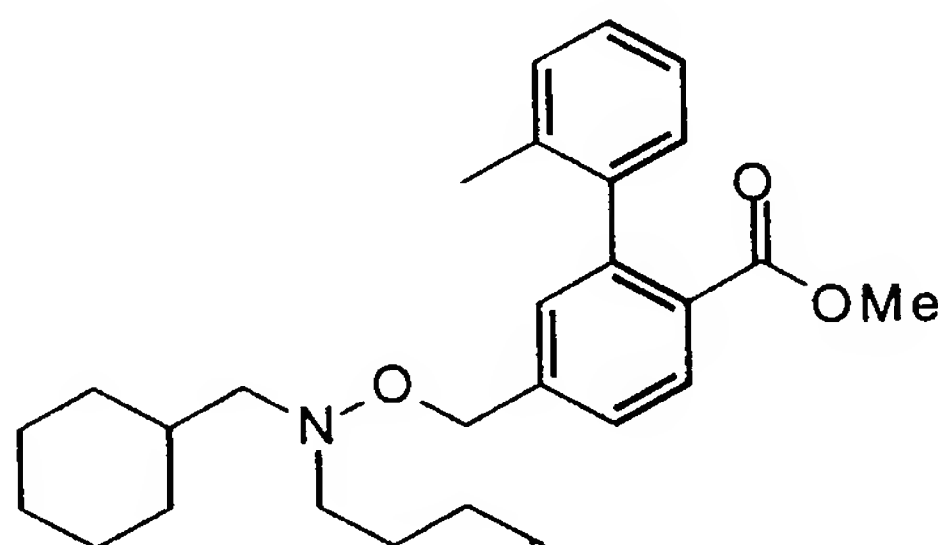
The desired product was prepared using the method described in Example 1176B starting with 4-phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1176A and cyclohexanecarboxaldehyde. m/e (ESI) 366 (MH<sup>+</sup>)

8995

Example 1186B4-N-(Cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

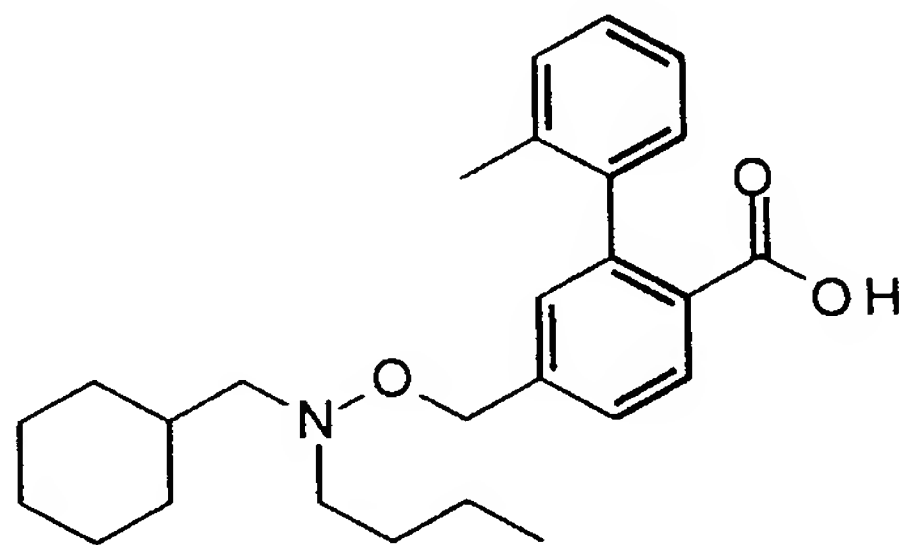
The desired product was prepared using the method described in Example 1176C starting with the compound in Example 1186A. m/e (ESI) 368 (MH<sup>+</sup>)

9000

Example 1186CN-[4-N--Butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester]

9005

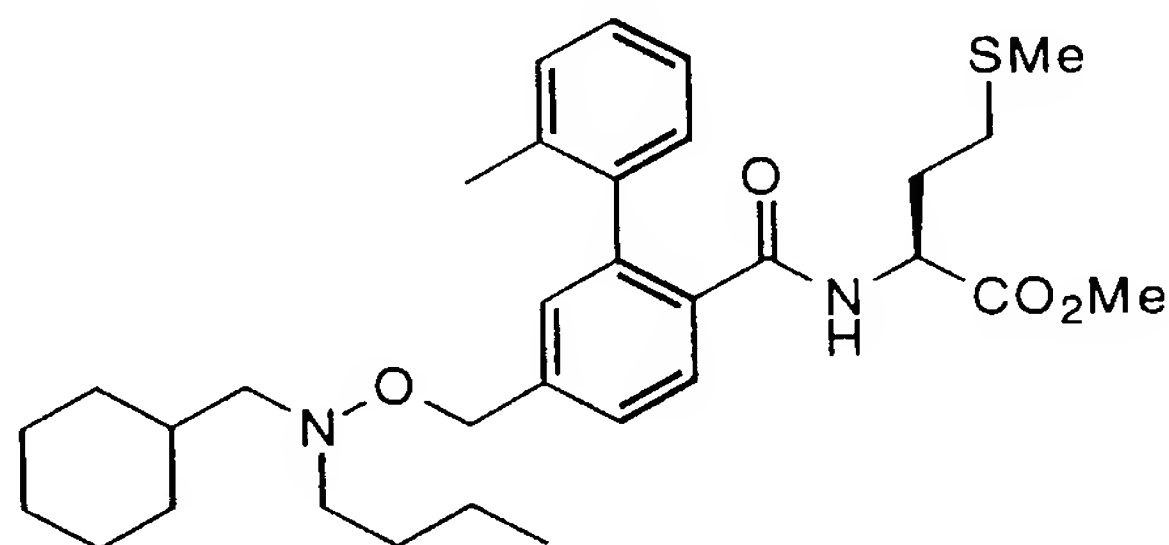
The desired product was prepared using the method described in Example 1176D starting with the compound in Example 1186B. m/e (ESI) 424 (MH<sup>+</sup>)

Example 1186D

9010

N-[4-N--Butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid

The desired product was prepared using the method described in Example 403E starting with the compound in Example 1186C.

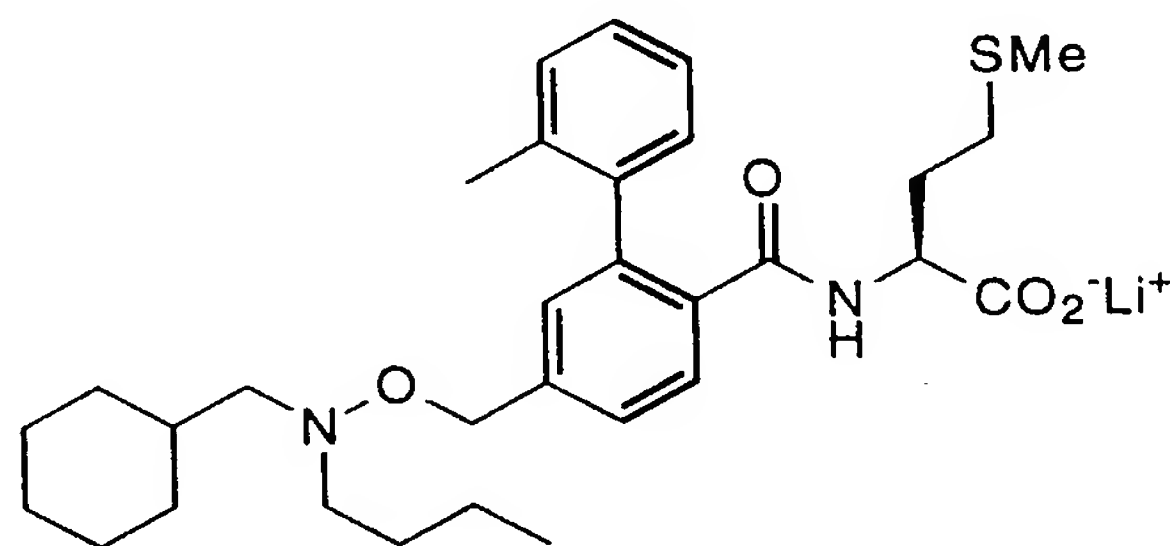


9015

Example 1186EN-[4-N--Butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired product was prepared using the method described in Example 403F starting with the compound in Example 1186D. m/e (ESI) 555 (MH<sup>+</sup>)

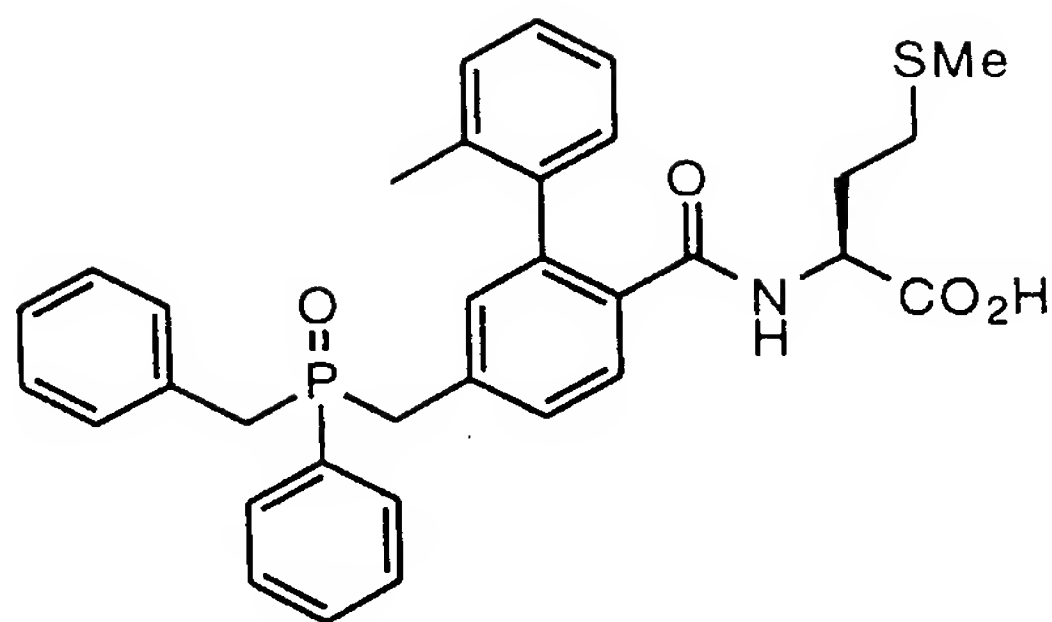
9020

Example 1186FN-[4-N--Butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

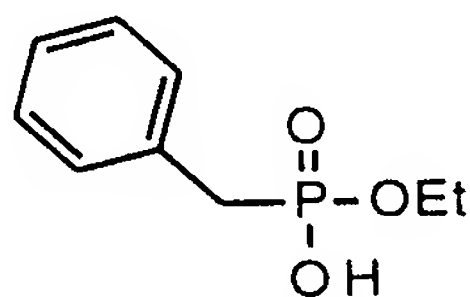
9025

The desired compound was prepared according to the method of Example 403I starting with the compound in Example 1186E. <sup>1</sup>H (300MHz, DMSO-d<sub>6</sub>, δ) 7.53 (1H, d, J=9Hz), 7.37 (1H, dd, J=7&2Hz), 7.30-7.05 (5H, m), 6.96 (1H, m), 4.63 (2H, s), 3.68 (1H, m), 2.62 (2H, t, J=8Hz), 2.42 (2H, d, J=8Hz), 2.25-1.95 (5H, m), 1.92 (3H, s), 1.80-1.50 (7H, m), 1.42 (3H, m), 1.26 (2H, m), 1.13 (3H, m), 0.85 (5H, t, J=8Hz). m/e (ESI) 539 (MH<sup>-</sup>) Anal.calc. for C<sub>31</sub>H<sub>43</sub>LiN<sub>2</sub>O<sub>4</sub>S·0.75 H<sub>2</sub>O C 66.46, H 8.01, N 5.00 Found C 66.43, H 8.02, N 4.88

9030



9035

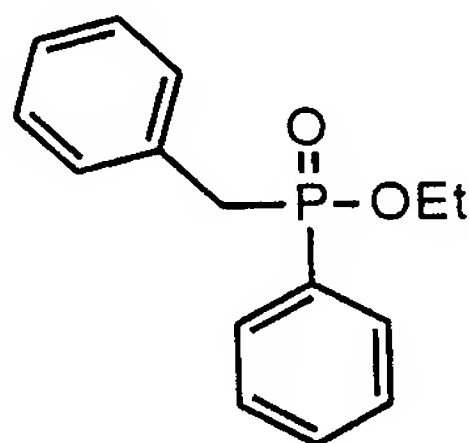
Example 1211N-[4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9040

Example 1211ABenzylphosphonic acid monoethyl ester

Diethyl benzylphosphonate (5.0 mL, 5.5 g, 24 mmol) was dissolved in absolute EtOH (25 mL), then 50% NaOH (3 mL) was added. The reaction was heated under reflux overnight, allowed to cool to RT, then partitioned between 2N HCl and EtOAc. Washed organic layer with brine, extracted combined aqueous layers with EtOAc, dried combined organic layers over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration recovered 4.5 g (93%). MS (DCI/NH<sub>3</sub>) 201/218 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

9045



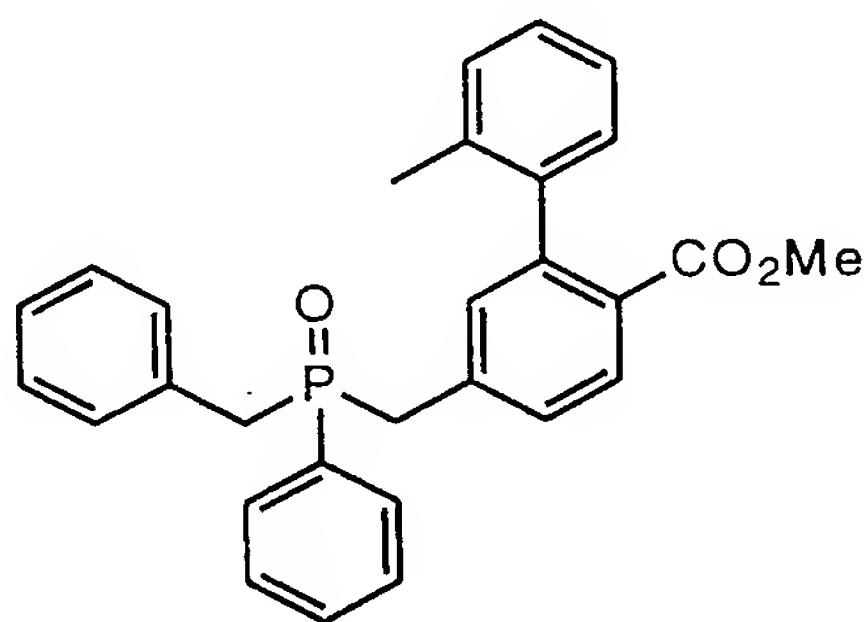
9050

Example 1211BBenzylphenylphosphonic acid ethyl ester

The compound described in Example 1211A (2.5 g, 12.5 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), cooled to 0-5 °C, then added DMF (50 µL) and oxalyl chloride (1.25 mL, 1.82 g, 14.3 mmol). After 15 min. removed the bath, and let the reaction warm to RT over 1 h. The reaction was then concentrated, dissolved in toluene, reconcentrated, dissolved in Et<sub>2</sub>O (8 mL), and cooled to -10 °C. Under N<sub>2</sub>, 3.0M phenylmagnesium chloride (3.3 mL) was added dropwise (removed bath after ca. 7 mL had been added

9055

because the reaction was too thick to stir). Stirred the reaction at RT for 3 h, then partitioned between 2N HCl and Et<sub>2</sub>O. Washed organic layer with water and brine, then dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration the compound was purified by chromatography using 1/4 hex/ EtOAc. Recovered 1.38 g (42%). MS (DCI/NH<sub>3</sub>) 261/278 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

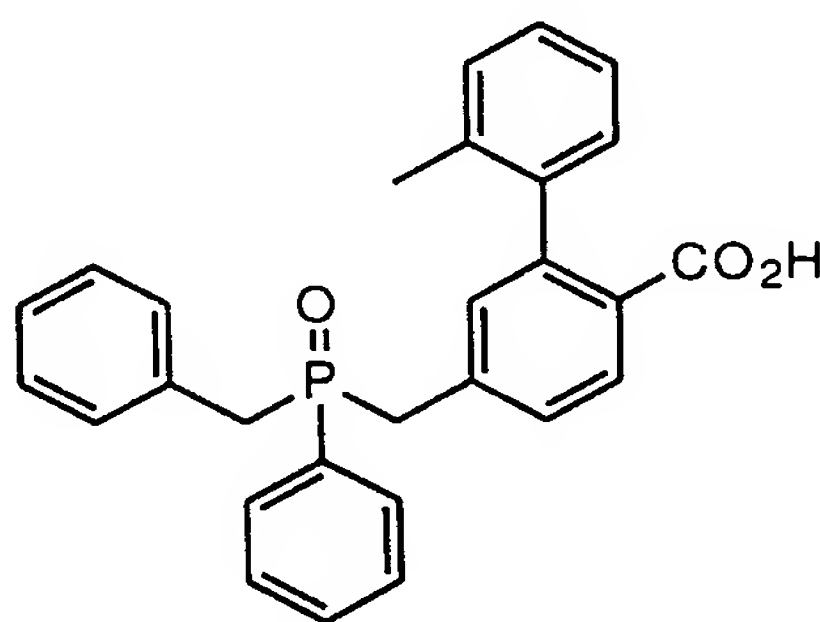


#### Example 1211C

##### 4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1211B and the bromide described in Example 1178D using the method found in JACS, **94**, 1774 (1972).

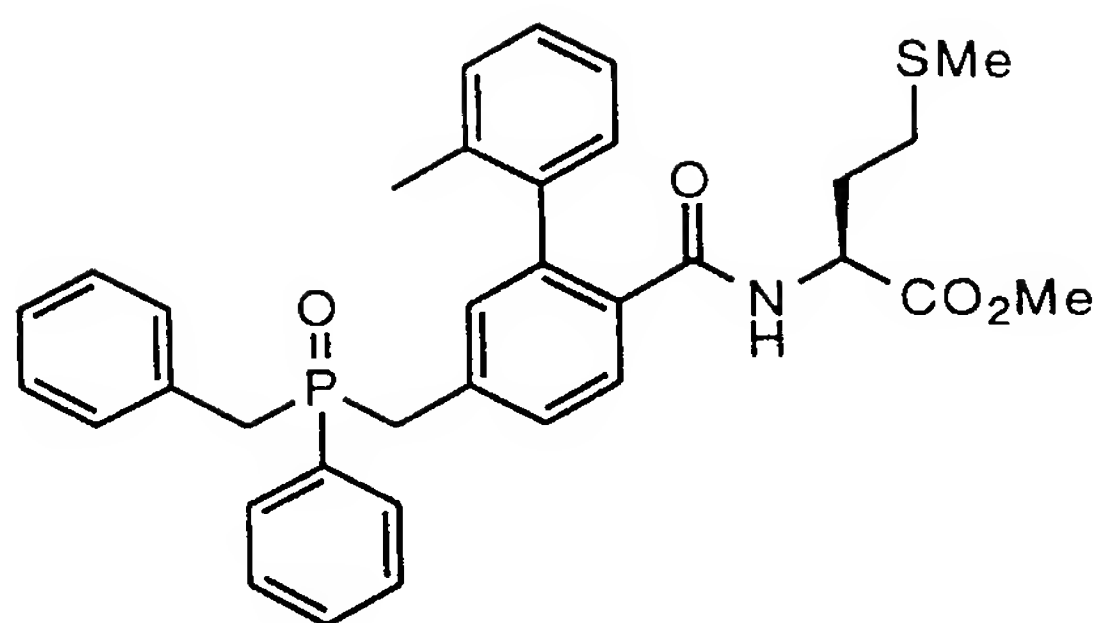
After chromatography using 1/2 hex/EtOAc the product still contained 35-40% (wt.) starting ethyl phosphinate. MS (APCI) 455 (M+H)<sup>+</sup> & 261 (M+H)<sup>+</sup> (for starting material).



#### Example 1211D

##### 4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1211C by the method of Example 1178H. The title compound was separated from the phosphinic acid by chromatography using 98/2/0.5 CHCl<sub>3</sub>/ MeOH/ CH<sub>3</sub>CO<sub>2</sub>H. MS (ESI) 439 (M-H)<sup>-</sup>.



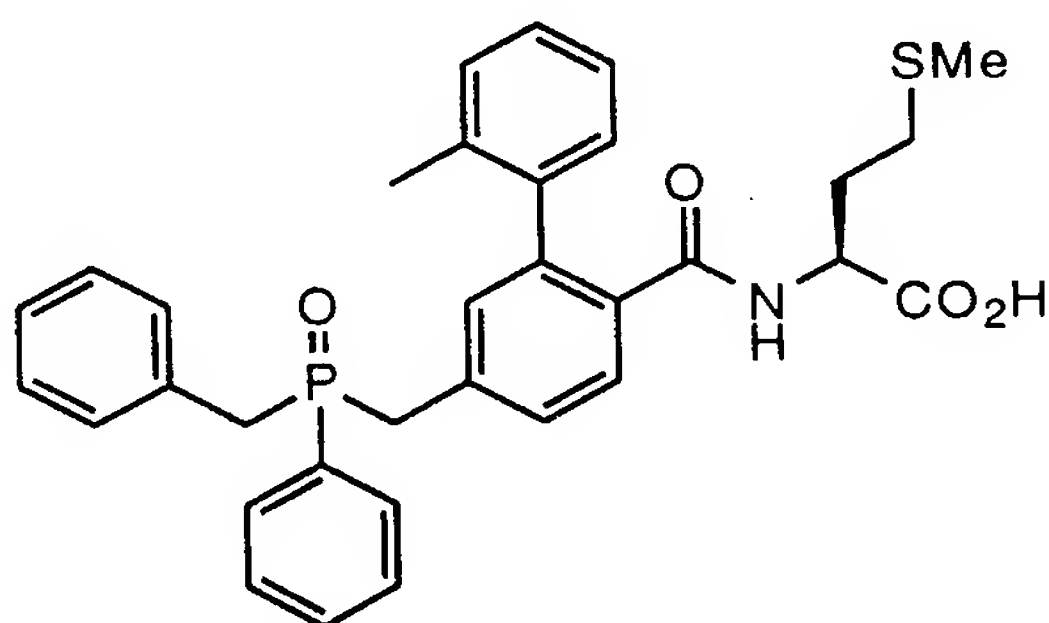
9080

Example 1211E

N-[4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9085

The title compound was prepared from the compound described in Example 1211D using the method of Example 1205D, except the chromatography used 1.5% EtOH in EtOAc. MS (APCI) 586 (M+H)<sup>+</sup>.

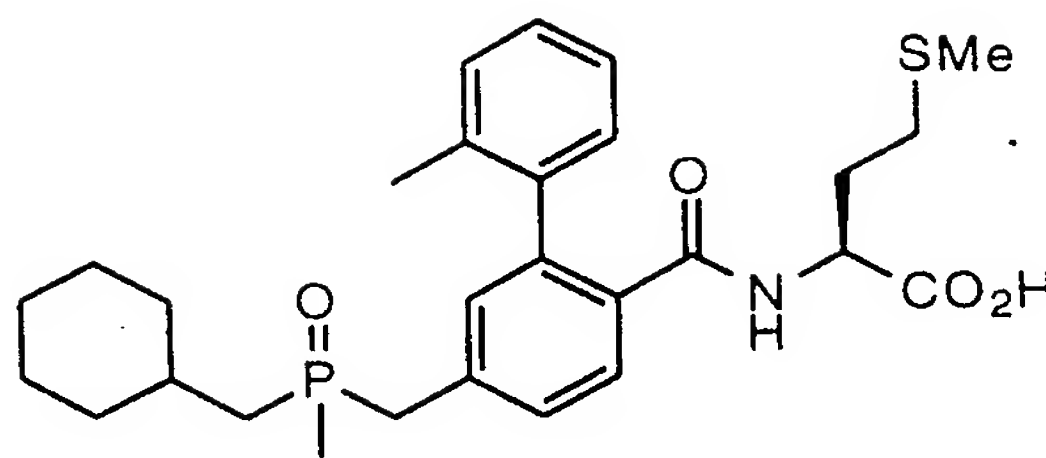
Example 1211F

9090

N-[4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

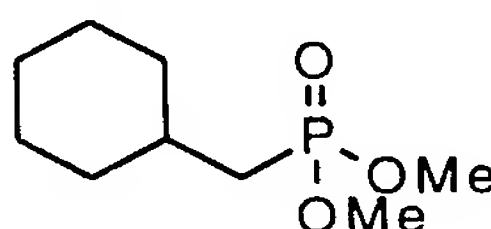
9095

The above compound was prepared from the compound described in Example 1211E according to the method of Example 1178J, except the lithium salt was not made. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.08 (m, 1H), 7.68 (m, 2H), 7.45 (m, 4H), 7.36 (d, 1H), 7.17, 7.10, 6.92, 6.82 (all m, total 10H), 4.19 (m, 1H), 3.50 (m, 4H), 2.10, 1.95, 1.80 (all m, total 10H). MS (ESI) 570 (M-H)<sup>-</sup>. Anal calcd for C<sub>33</sub>H<sub>34</sub>NO<sub>4</sub>PS·0.15 CHCl<sub>3</sub>: C, 67.53; H, 5.84; N, 2.38. Found: C, 67.55; H, 5.90; N, 2.24.



Example 1212

N-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

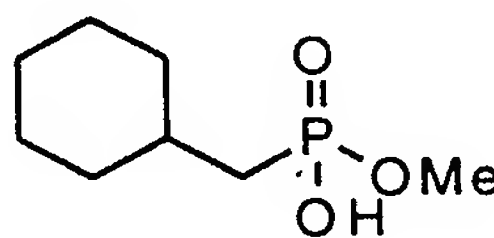


Example 1212A

Cyclohexylmethylphosphonic acid dimethyl ester

Using the Grignard reagent made from bromomethyl cyclohexane and dimethyl phosphochloridate, the title compound was prepared by the method found in Engel, Robert, ed. Synthesis of Carbon-Phosphorous Bonds, p. 179. Boca Raton, FL: CRC Press, 1988.

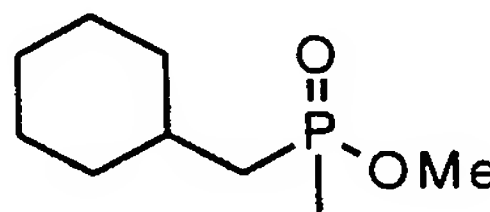
The compound was purified by chromatography using EtOAc. MS (DCI/NH<sub>3</sub>) 207/224 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



Example 1212B

Cyclohexylmethylphosphonic acid monomethyl ester

The title compound was prepared from the compound described in Example 1212A by the method of Example 1211A. MS (DCI/NH<sub>3</sub>) 193/210 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

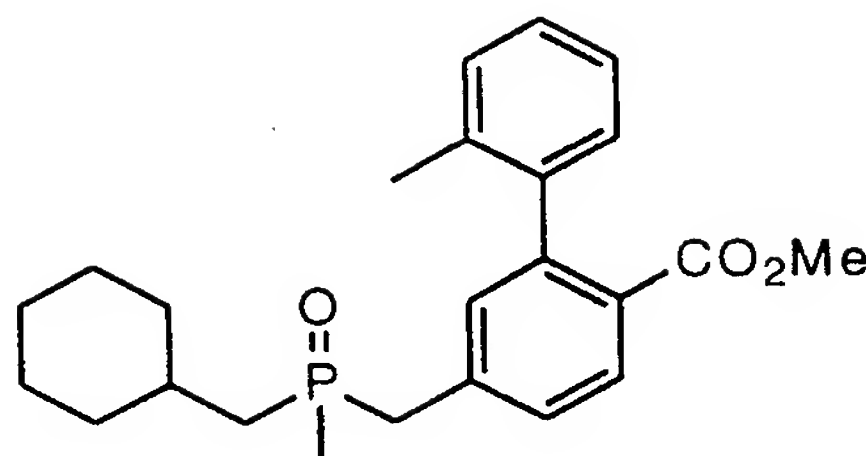


Example 1212C

(Cyclohexylmethyl)methylphosphinic acid methyl ester

The title compound was prepared from the compound described in Example 1212B and methylmagnesium bromide by the method of Example 1211B. MS (DCI/NH<sub>3</sub>) 191/208 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

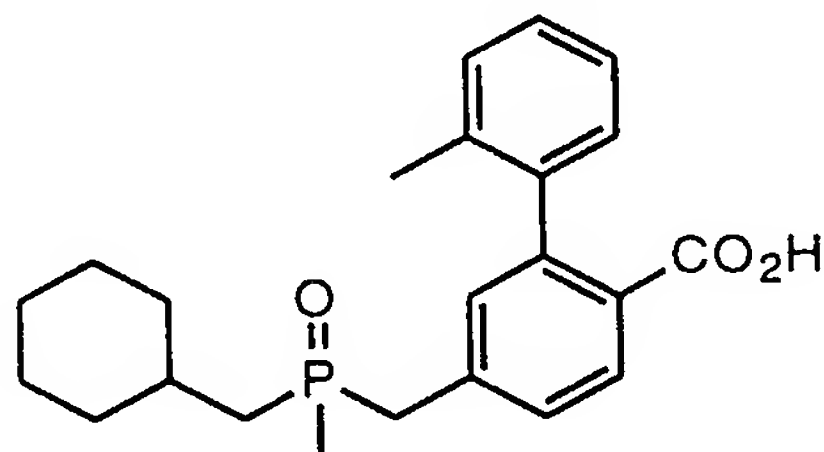
9125

Example 1212D

4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

9130

The title compound was prepared from the compound described in Example 1212C and the bromide described in Example 1178D using the method found in JACS, **94**, 1774 (1972), followed by purification with chromatography using EtOAc/EtOH 93/7. MS (DCI/NH<sub>3</sub>) 399/416 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



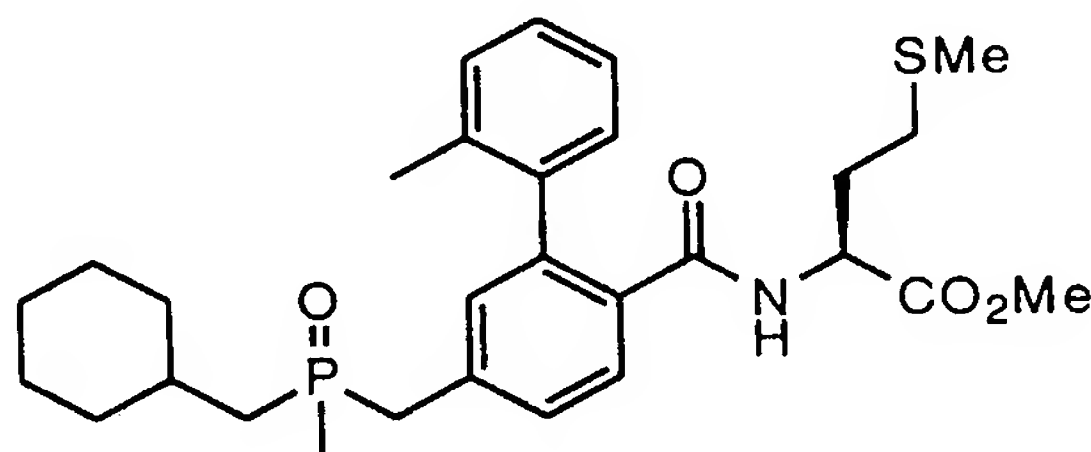
9135

Example 1212E

4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1212D using the method of Example 1178H. MS (DCI/NH<sub>3</sub>) 385/402 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

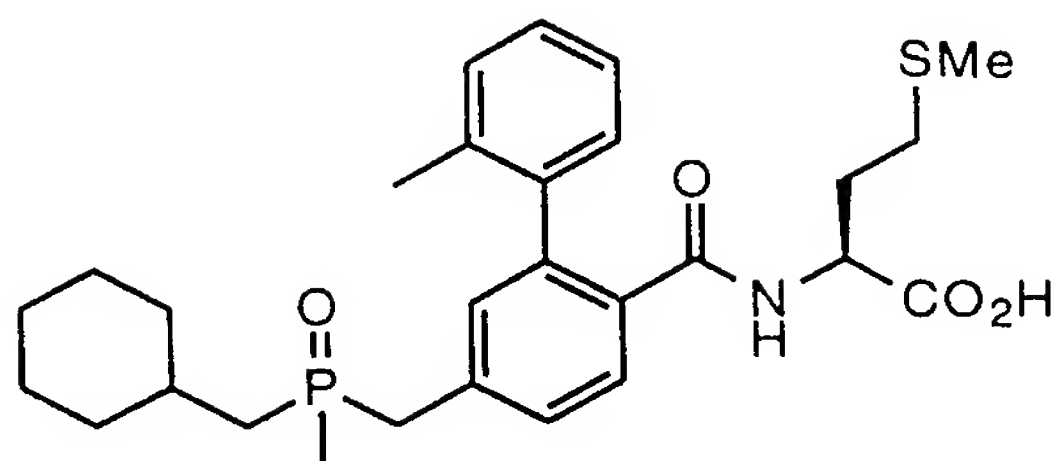
9140

Example 1212F

N-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9145

The above compound was prepared from the compound described in Example 1212E according to the method of Example 1205D. MS (APCI) 530 (M+H)<sup>+</sup>.

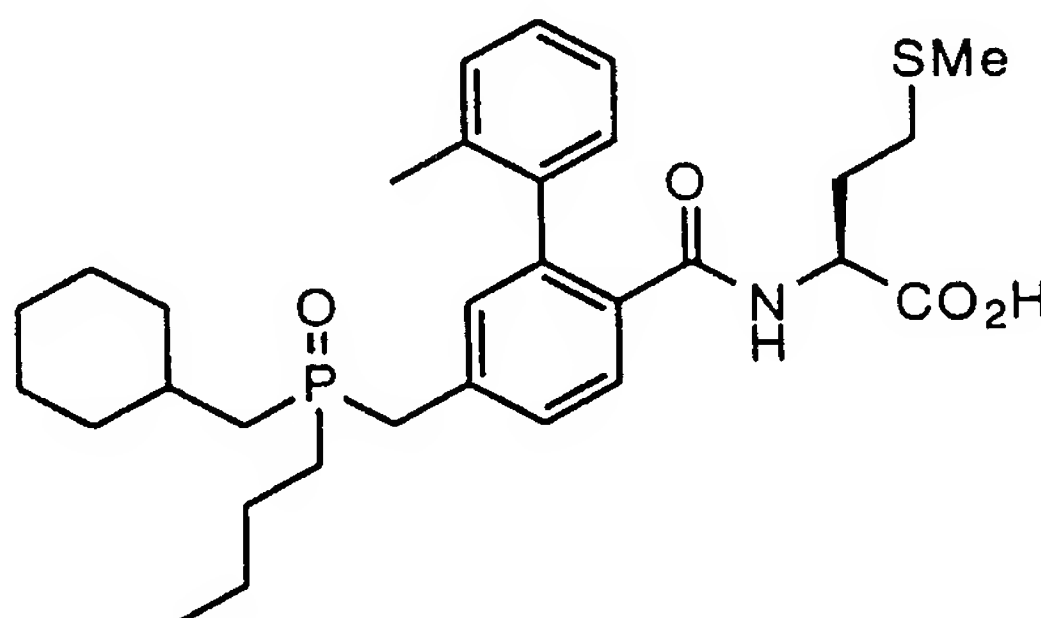
Example 1212G

9150

N-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9155

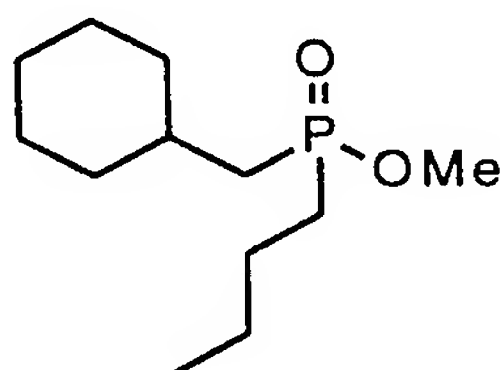
The above compound was prepared from the compound described in Example 1212F according to the method of Example 1178J, except the lithium salt was not made. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.08 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (dd, 2H), 2.10 (m, 5H), 1.95 (s, 3H), 1.80, 1.60 (both m, total 10H), 1.30 (d, 3H), 1.20, 1.00 (both m, total 5H). MS (ESI) 514 (M-H)<sup>-</sup>. Anal calcd for C<sub>28</sub>H<sub>38</sub>NO<sub>4</sub>PS: C, 65.22; H, 7.43; N, 2.72. Found: C, 64.86; H, 7.44; N, 2.60.



9160

Example 1213

N-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine



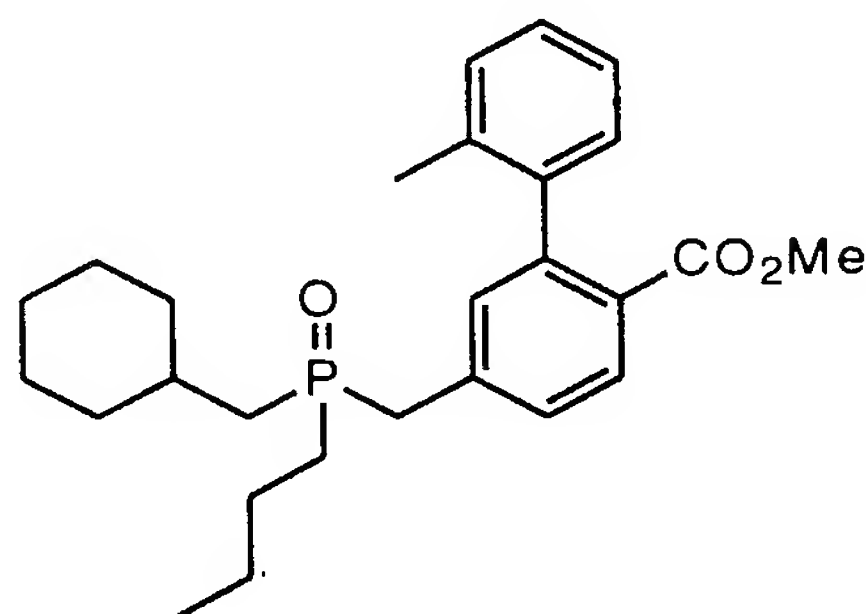
9165

Example 1213A

(Cyclohexylmethyl)butylphosphinic acid methyl ester



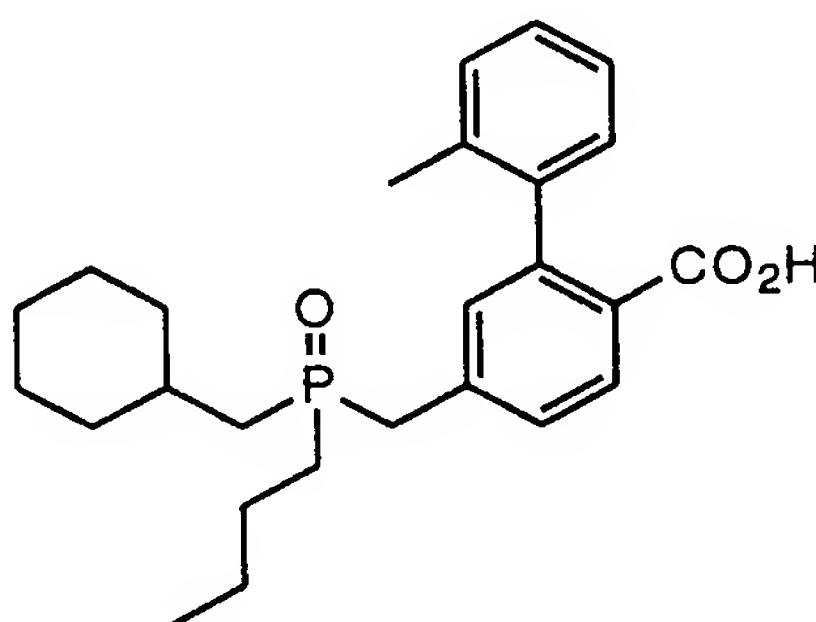
The title compound was prepared from the compound described in Example 1212B and butylmagnesium chloride by the method of Example 1211B. MS (DCI/NH<sub>3</sub>) 233/250 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



Example 1213B

4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

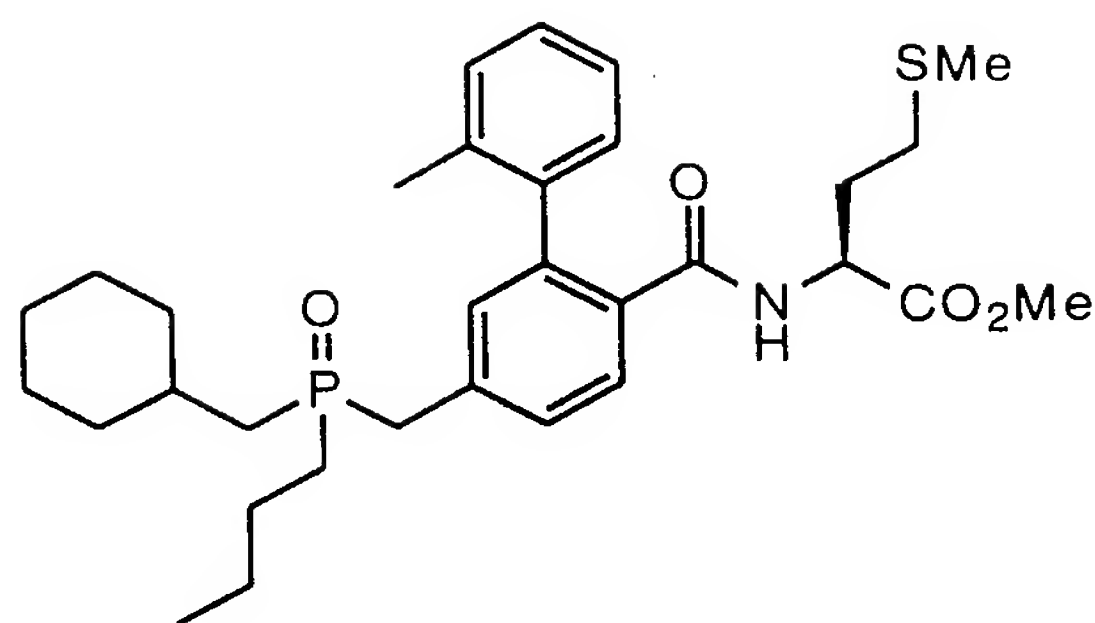
The title compound was prepared from the compound described in Example 1213A and the bromide described in Example 1178D using the method of Example 1212D. MS (DCI/NH<sub>3</sub>) 441/458 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



Example 1213C

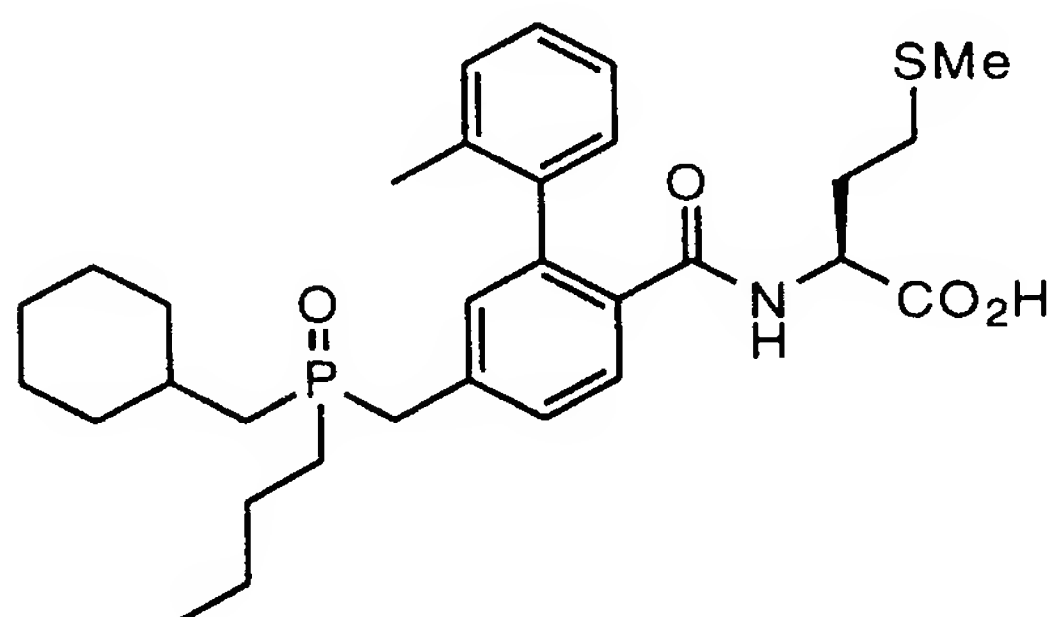
4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1213B using the method of Example 1178H. MS (DCI/NH<sub>3</sub>) 427/444 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

Example 1213D

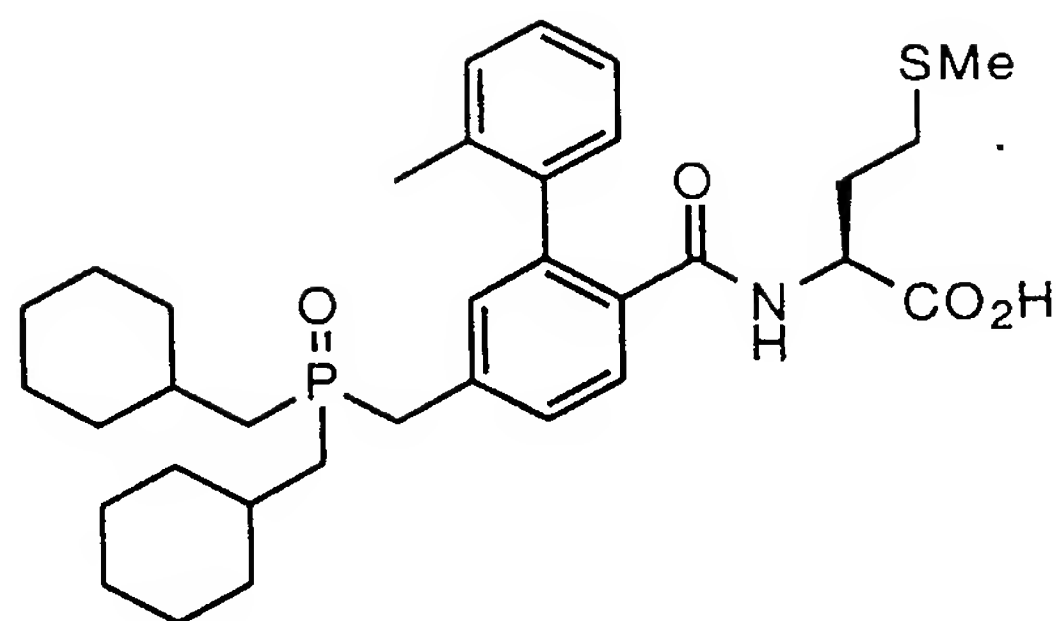
N-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9190 The above compound was prepared from the compound described in Example 1213C according to the method of Example 1205D. MS (APCI) 572 (M+H)<sup>+</sup>.

Example 1213E

9195 N-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

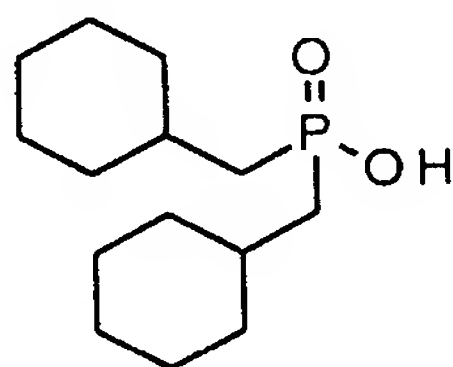
The above compound was prepared from the compound described in Example 1213D according to the method of Example 1178J, except the lithium salt was not made. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.08 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.85-0.90 (envelope 21H), 0.85 (t, 3H). MS (ESI) 556 (M-H)<sup>-</sup>. Anal calcd for C<sub>31</sub>H<sub>44</sub>NO<sub>4</sub>PS: C, 66.76; H, 7.95; N, 2.51. Found: C, 66.73; H, 8.00; N, 2.42.



9205

Example 1214

N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

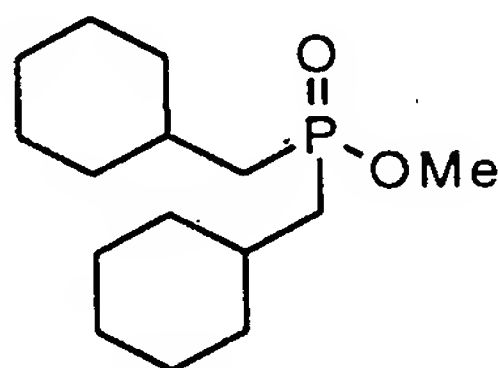


9210

Example 1214ADi(cyclohexylmethyl)phosphinic acid

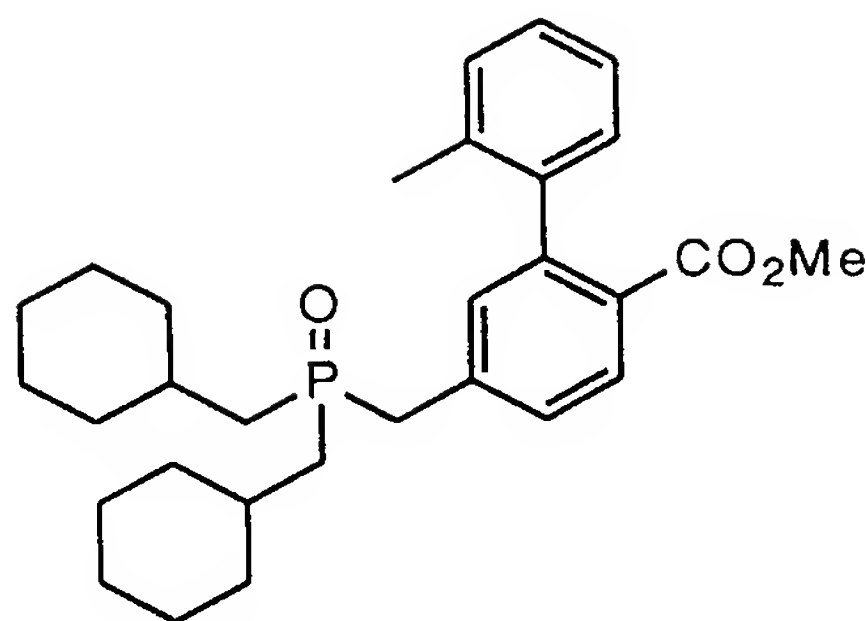
Using the Grignard reagent made from bromomethyl cyclohexane, the title compound was prepared by the method found in JACS, **72**, 5508 (1950). MS (DCI/NH<sub>3</sub>) 259/276 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

9215

Example 1214BDi(cyclohexylmethyl)phosphinic acid methyl ester

Using the compound described in Example 1214A, the title compound was prepared by the method found in JOC, **59**, 7616 (1994)-specifically Method B on p. 7623. MS (DCI/NH<sub>3</sub>) 273/290 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

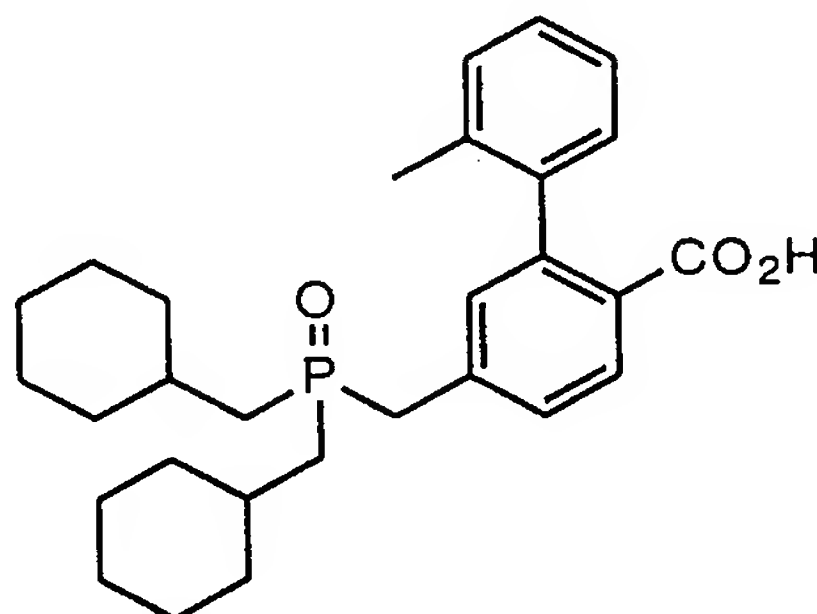
9220

Example 1214C

9225 4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

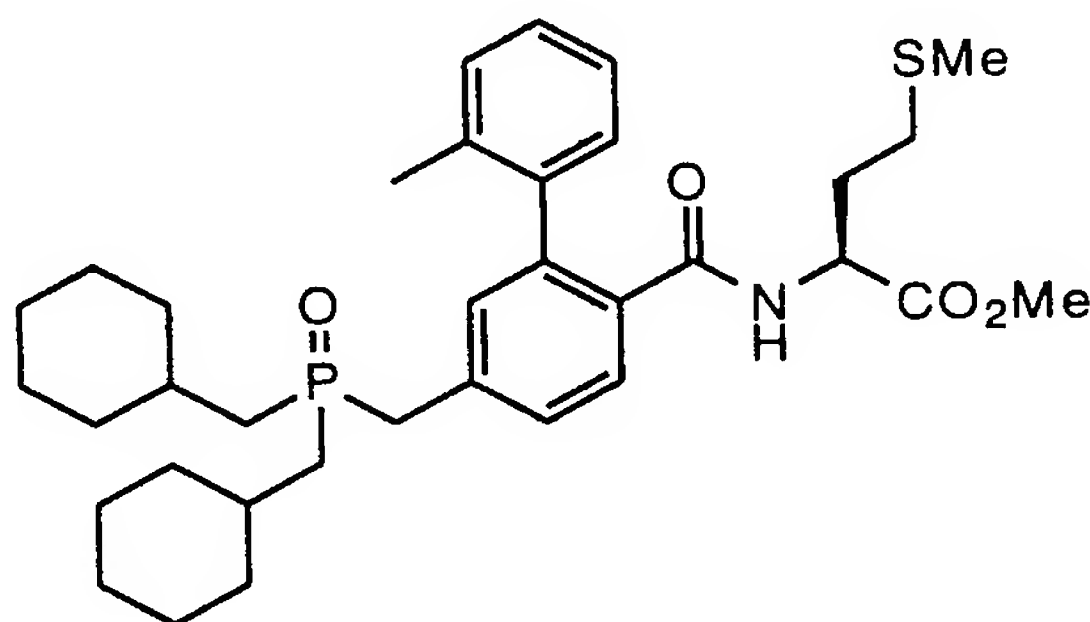
The title compound was prepared from the compound described in Example 1214B and the bromide described in Example 1178D using the method of Example 1212D. MS (APCI) 481 (M+H)<sup>+</sup>.

9230

Example 1214D

4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

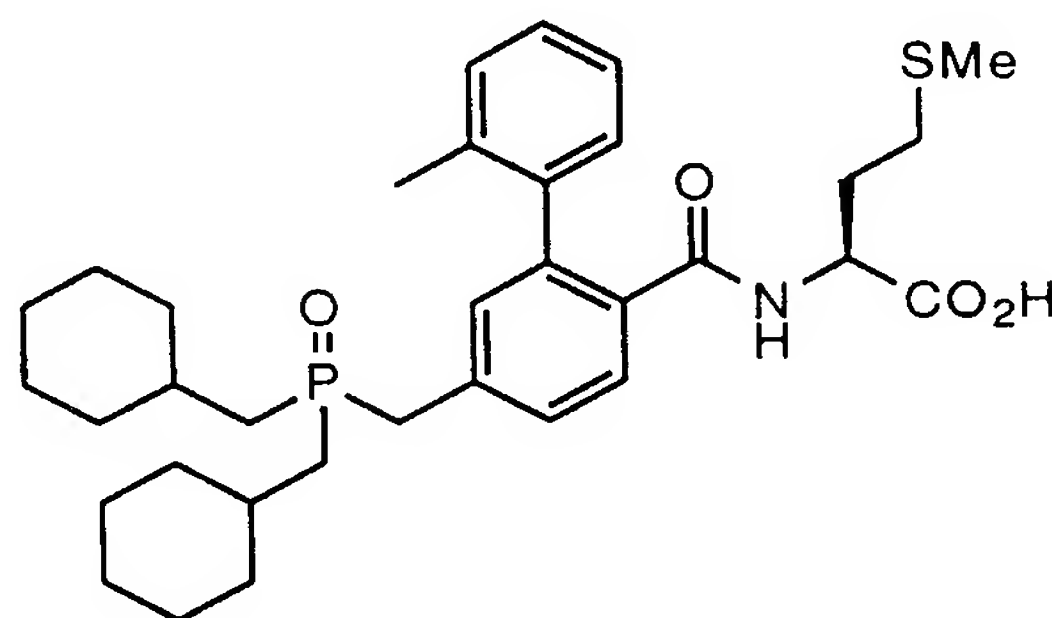
9235 The title compound was prepared from the compound described in Example 1214C using the method of Example 1178H. MS (APCI) 467 (M+H)<sup>+</sup>.

Example 1214E

N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9240

The above compound was prepared from the compound described in Example 1214D according to the method of Example 1205D. MS (APCI) 612 (M+H)<sup>+</sup>.



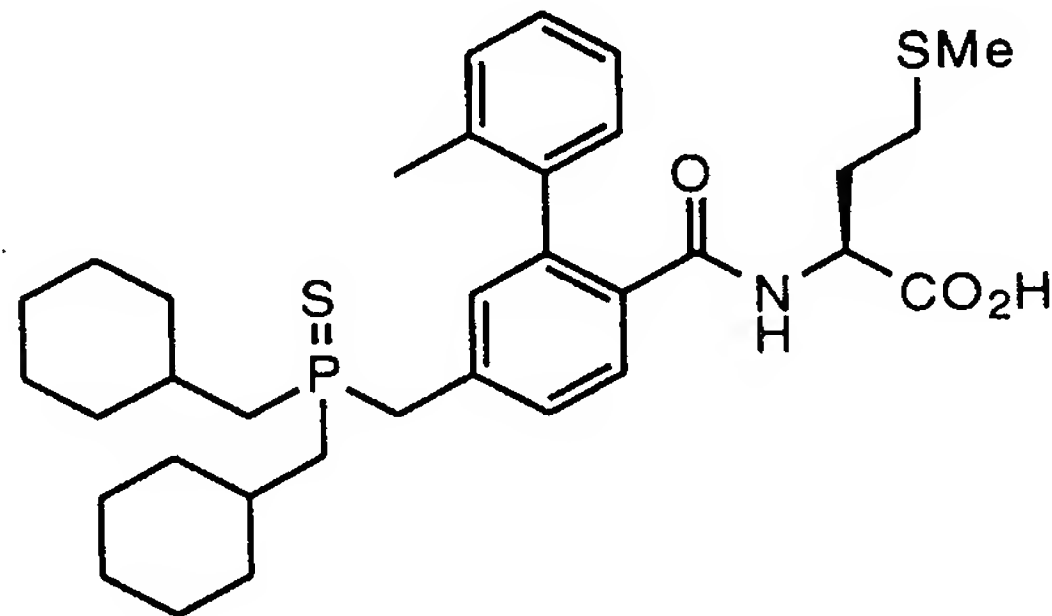
9245

Example 1214F

N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1214E according to the method of Example 1178J, except the lithium salt was not made. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.04 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 18H), 1.20 (m, 6H), 0.95 (m, 4H). MS (ESI) 596 (M-H)<sup>-</sup>. Anal calcd for C<sub>34</sub>H<sub>48</sub>NO<sub>4</sub>PS: C, 68.31; H, 8.09; N, 2.34. Found: C, 68.20; H, 8.19; N, 2.36.

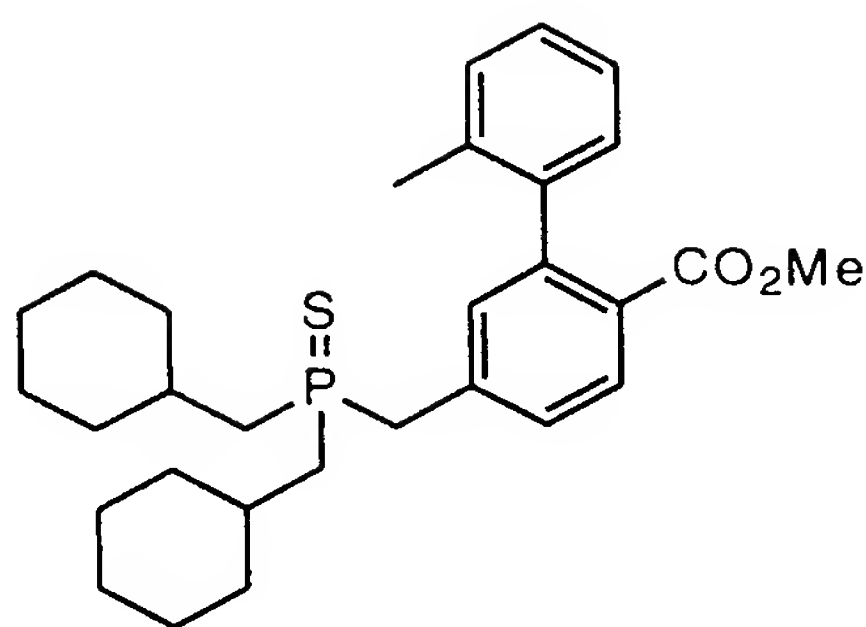
9250



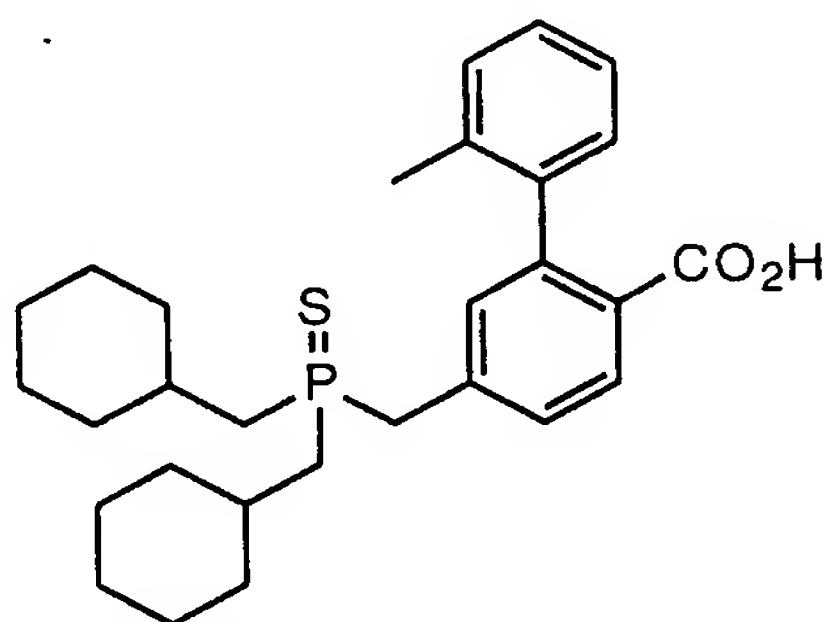
9255

Example 1215

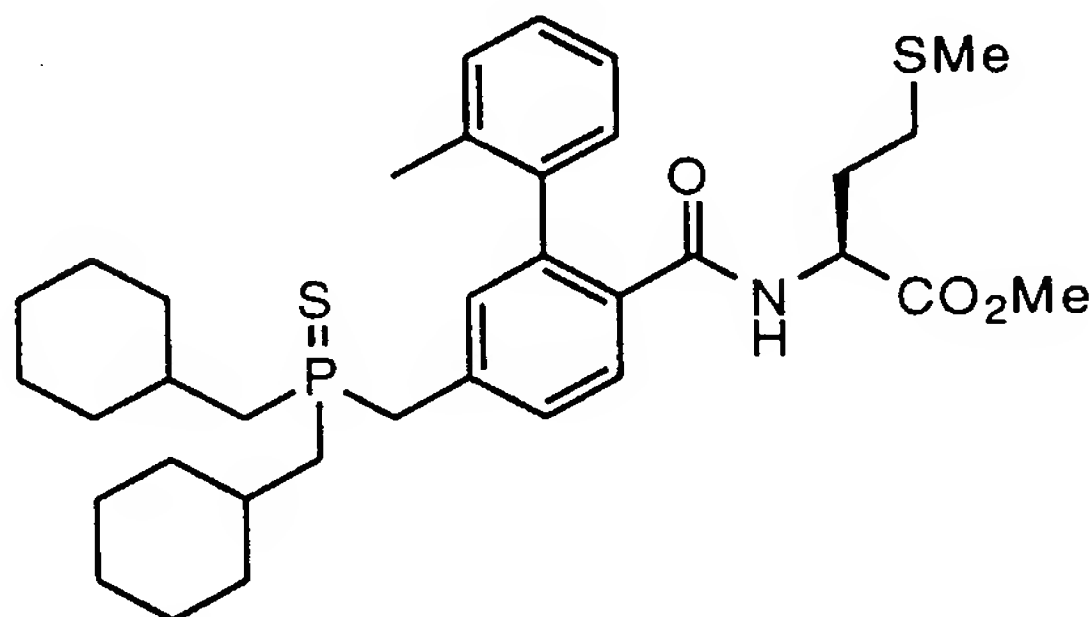
N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

Example 1215A4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The compound described in Example 1214C (390 mg, 0.81 mmol) was dissolved in CH<sub>3</sub>CN (15 mL), then Lawesson's reagent (1.57 g, 3.88 mmol) was added. The reaction was heated under reflux for 3 h, then stirred at RT overnight. After filtration through celite and concentration of the filtrate, purification by chromatography using hex/EtOAc 85/15 gave 335 mg (83%) of the title compound. MS (APCI) 497 (M+H)<sup>+</sup>.

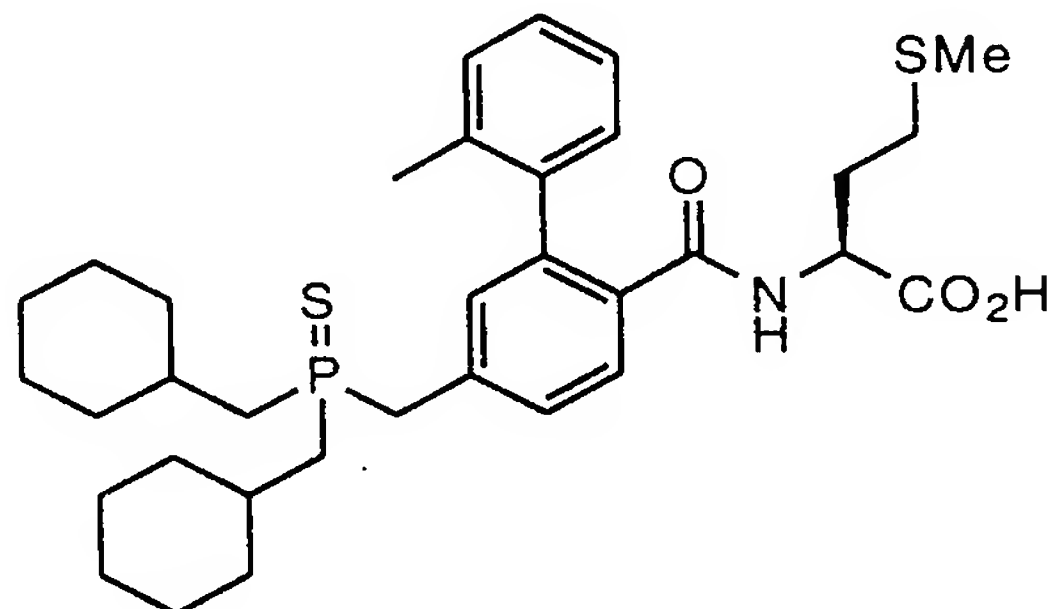
Example 1215B4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1215A using the method of Example 1178H. MS (ESI) 483 (M+H)<sup>+</sup>.

Example 1215C

N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

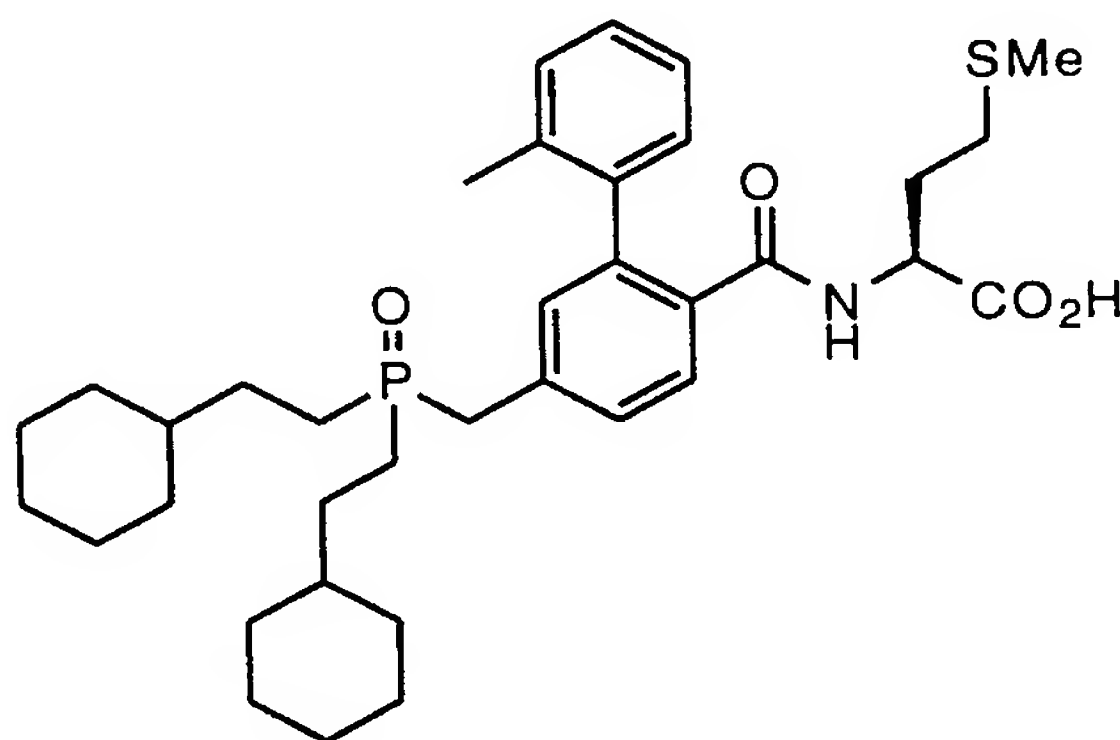
The above compound was prepared from the compound described in Example 1215B according to the method of Example 1205D. MS (APCI) 628 (M+H)<sup>+</sup>.



Example 1215D

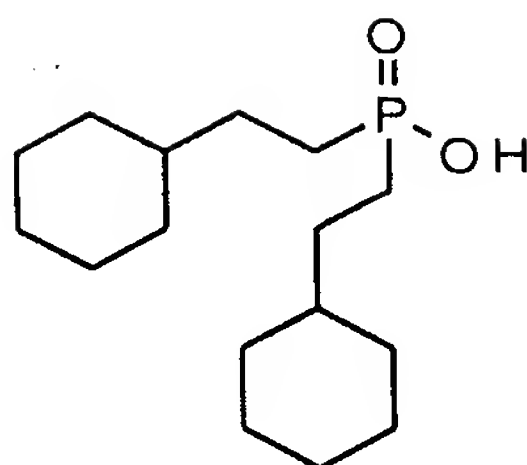
N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1215C according to the method of Example 1178J, except the lithium salt was not made. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.14 (d, 1H), 7.46 (d, 1H), 7.38 (d, 1H), 7.20, 7.14 (both m, total 5H), 4.21 (m, 1H), 3.40 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 18H), 1.20, 1.00 (both m, total 10H). MS (ESI) 612 (M-H)<sup>-</sup>. Anal calcd for C<sub>34</sub>H<sub>48</sub>NO<sub>3</sub>PS<sub>2</sub>: C, 66.53; H, 7.88; N, 2.28. Found: C, 66.26; H, 7.86; N, 2.19.

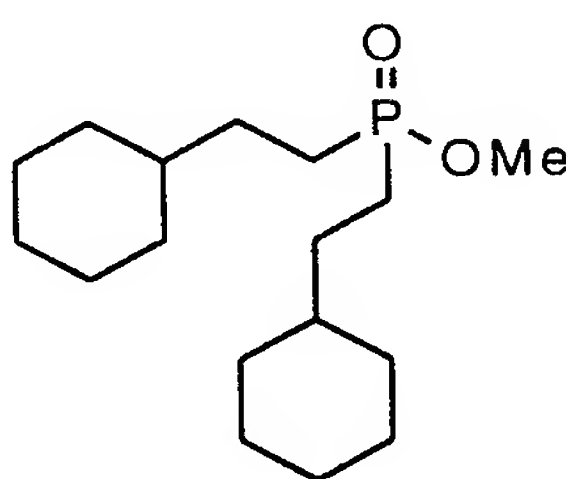


Example 1219

N-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

Example 1219ADi(2-cyclohexylethyl)phosphinic acid

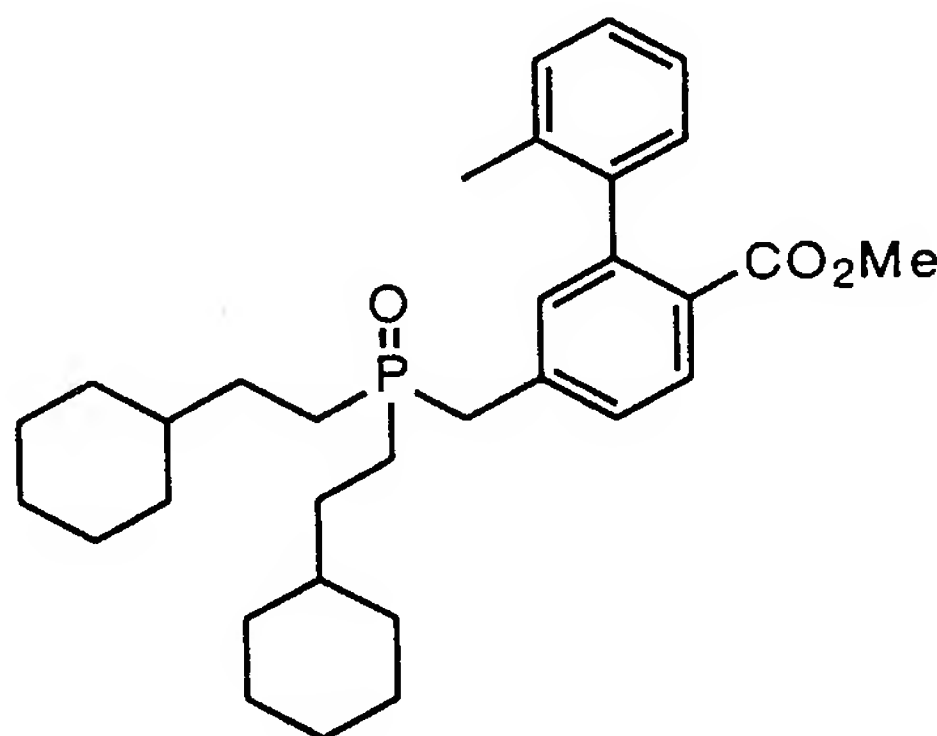
9300 The bromide described in Example 1207A was converted to the Grignard reagent, then used to prepare the title compound by the method of Example 1214A. MS (DCI/NH<sub>3</sub>) 287/304 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



9305

Example 1219BDi(2-cyclohexylethyl)phosphinic acid methyl ester

Using the compound described in Example 1219A, the title compound was prepared by the method of Example 1214B. MS (DCI/NH<sub>3</sub>) 301/318 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



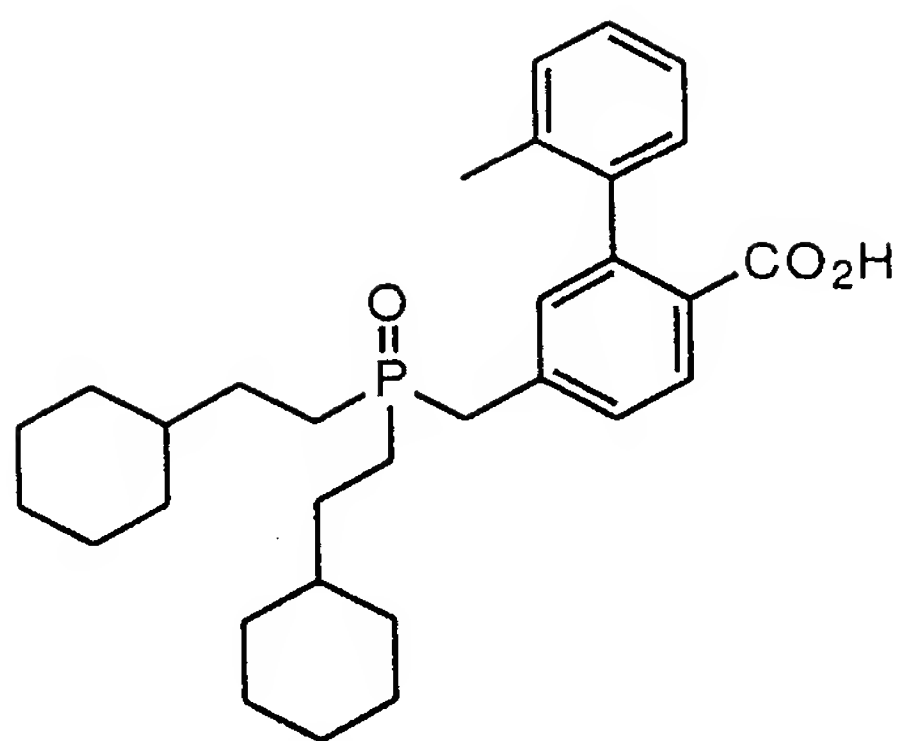
9310

Example 1219C

4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

9315 The title compound was prepared from the compound described in Example 1219B and the bromide described in Example 1178D using the method of Example 1212D. MS (APCI) 509 (M+H)<sup>+</sup>.

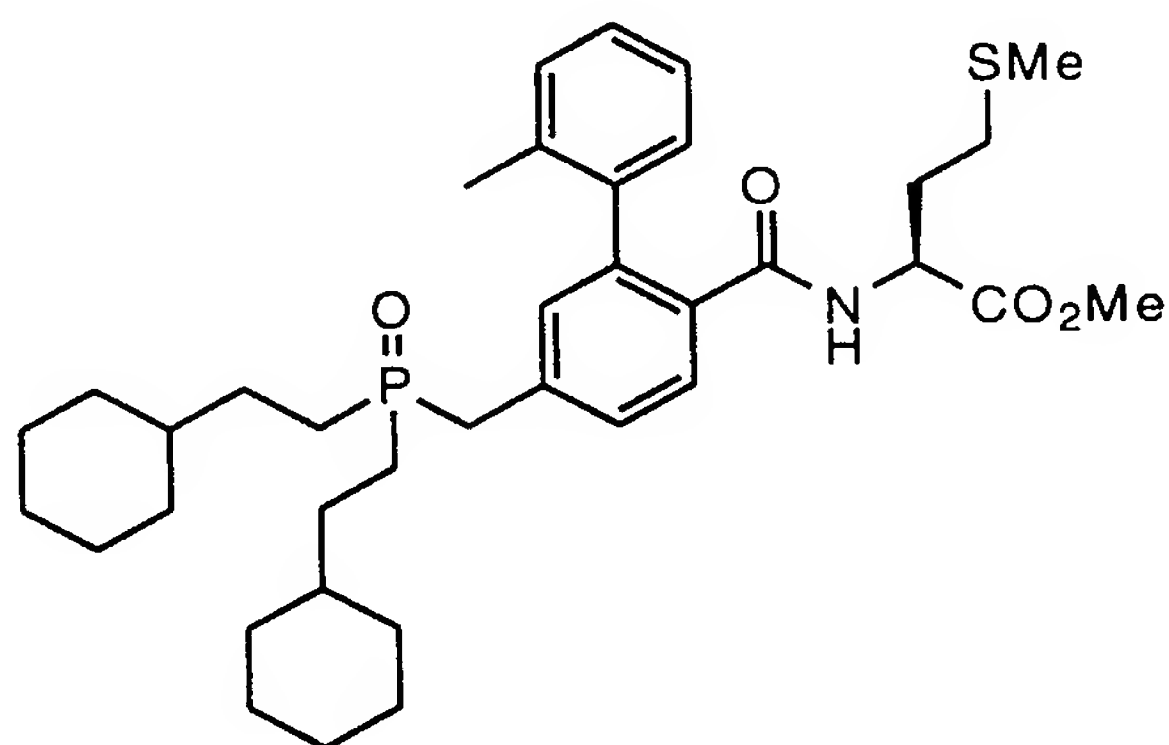


Example 1219D

9320

4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1219C using the method of Example 1178H. MS (APCI) 495 (M+H)<sup>+</sup>.

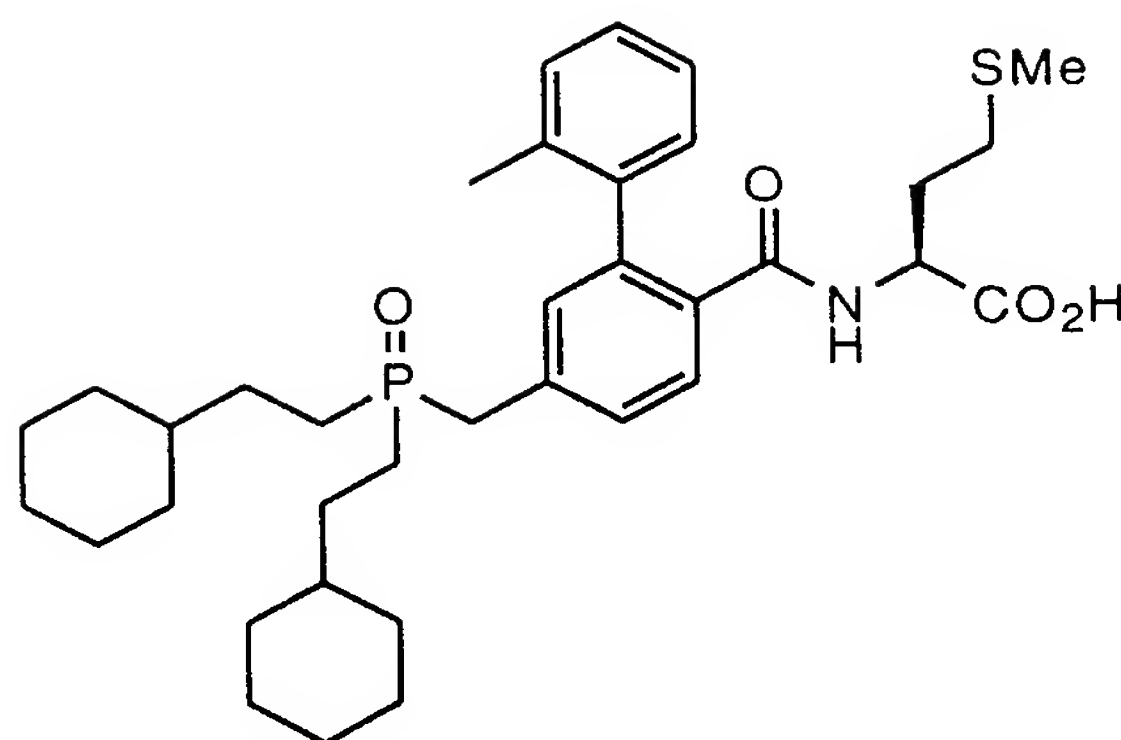
Example 1219E

9325

N-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

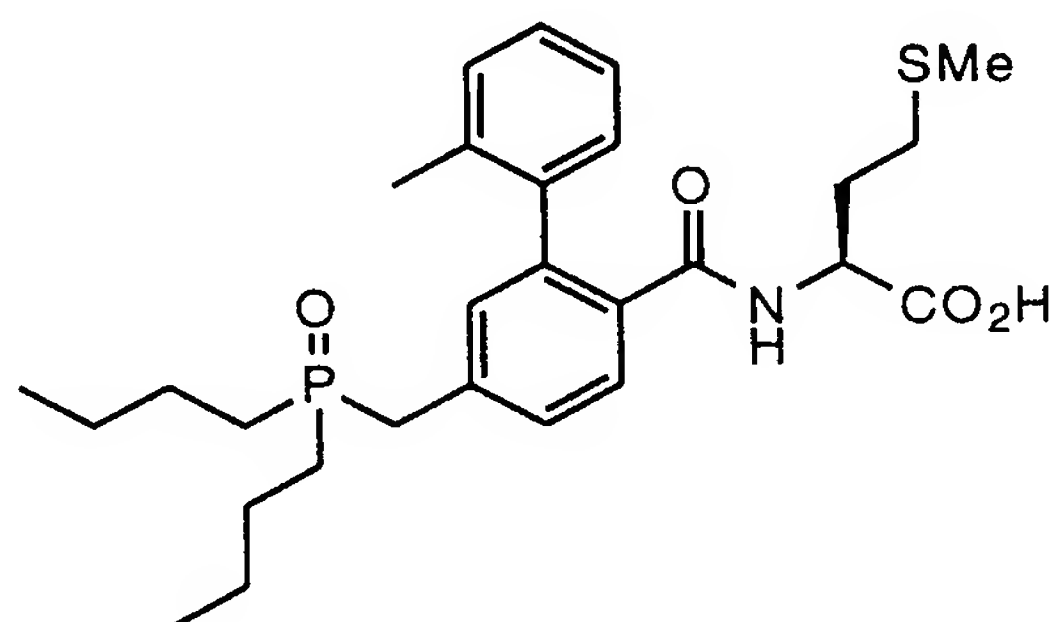
The above compound was prepared from the compound described in Example 1219D according to the method of Example 1205D. MS (APCI) 640 (M+H)<sup>+</sup>.

9330

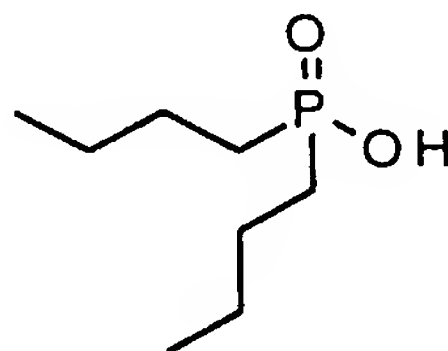
Example 1219FN-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9335 The above compound was prepared from the compound described in Example 1219E according to the method of Example 1178J, except the lithium salt was not made. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.07 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 16H), 1.32 (m, 4H), 1.15 (m, 8H), 0.83 (m, 4H). MS (ESI) 624 (M-H)<sup>-</sup>. Anal calcd for C<sub>36</sub>H<sub>52</sub>NO<sub>4</sub>PS: C, 69.09; H, 8.37; N, 2.24. Found: C, 68.98; H, 8.33; N, 2.20.

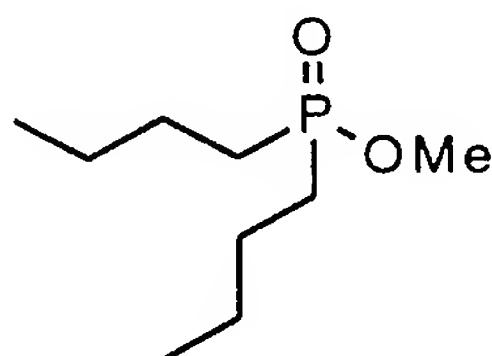
9340

Example 1222N-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9345

Example 1222ADibutylphosphinic acid

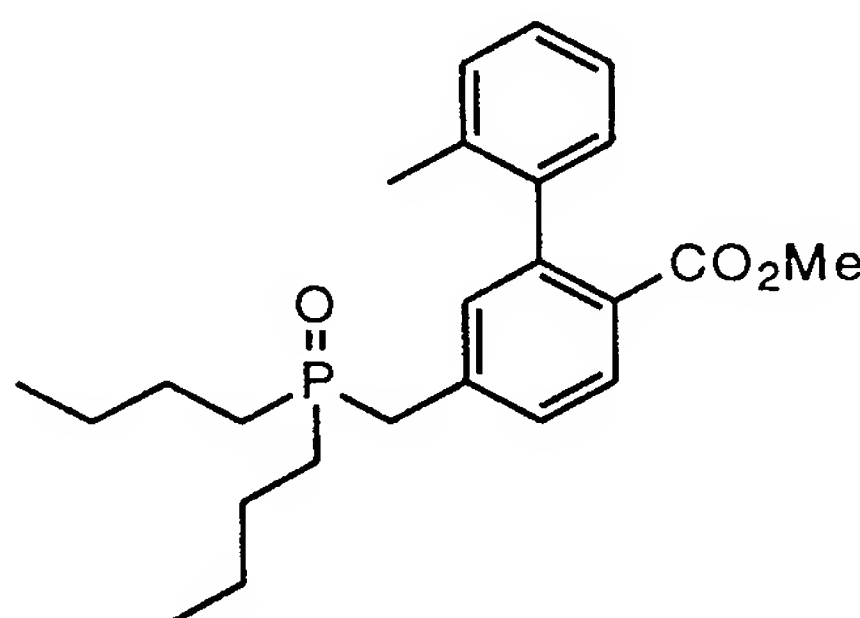
Using butylmagnesium chloride, the title compound was prepared by the method of  
 9350 Example 1214A. MS (DCI/NH<sub>3</sub>) 179/196 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



Example 1222B

Dibutylphosphinic acid methyl ester

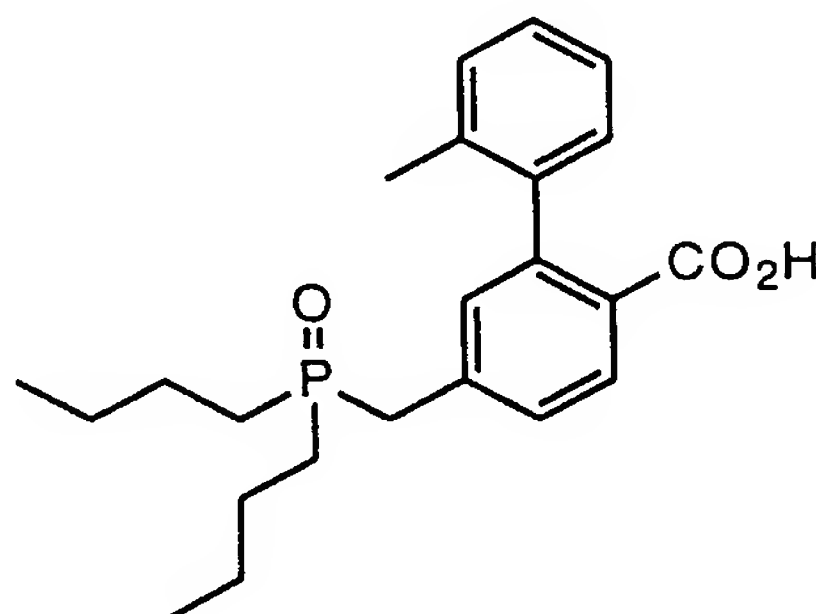
9355 Using the compound described in Example 1222A, the title compound was prepared  
 by the method of Example 1214B. MS (DCI/NH<sub>3</sub>) 193/210 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.



Example 1222C

9360 4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1222B  
 and the bromide described in Example 1178D using the method of Example 1212D. MS  
 (DCI/NH<sub>3</sub>) 401/418 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

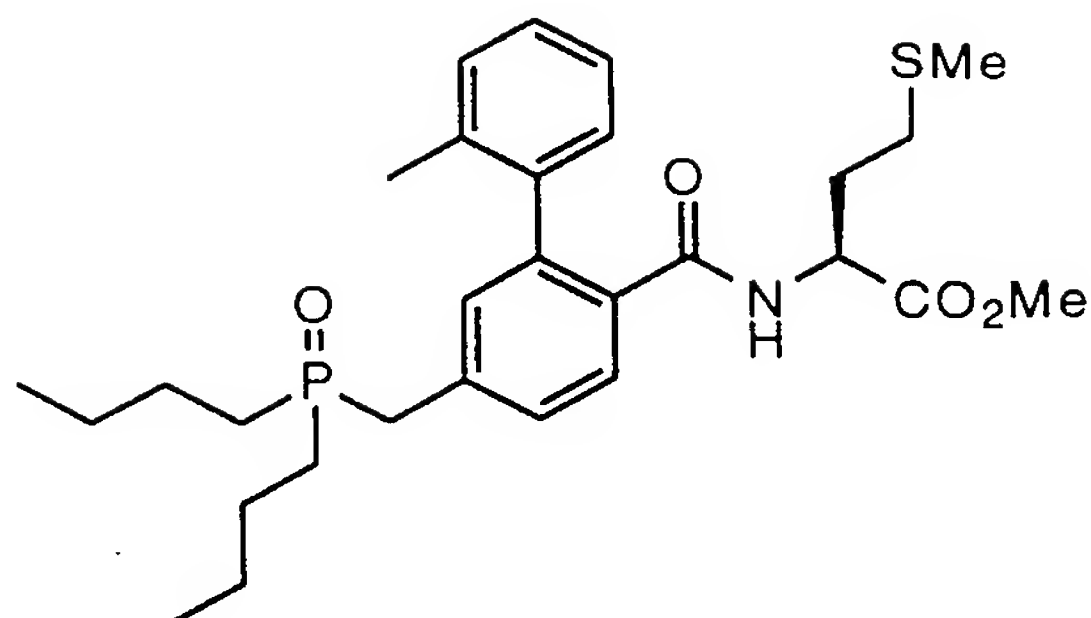


Example 1222D

4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

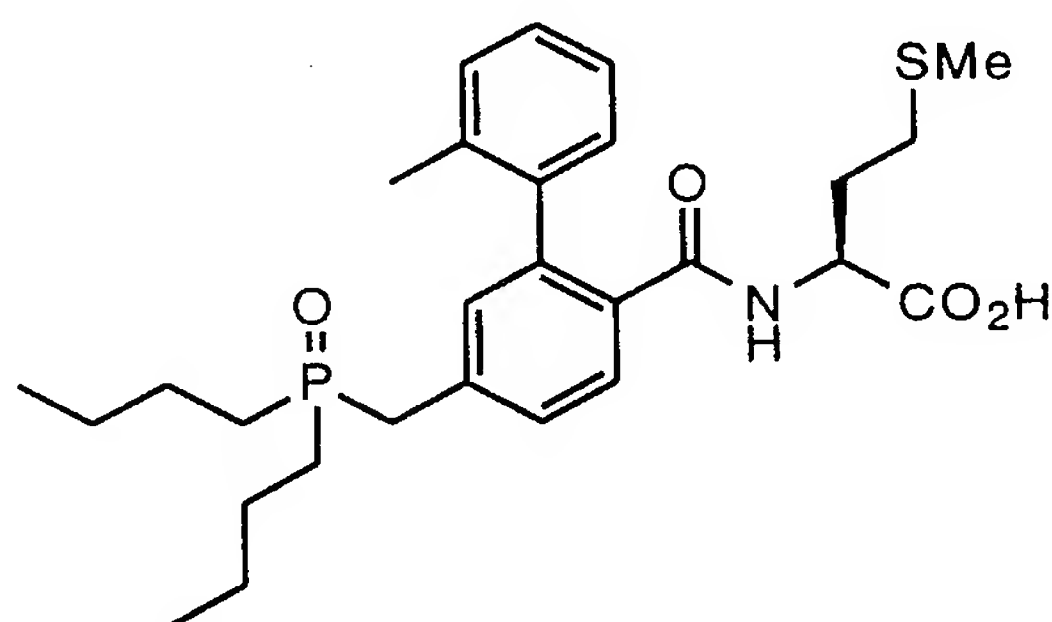
9365 The title compound was prepared from the compound described in Example 1222C  
 using the method of Example 1178H. MS (DCI/NH<sub>3</sub>) 387/404 (M+H)<sup>+</sup>/ (M+H+NH<sub>3</sub>)<sup>+</sup>.

9370

Example 1222E

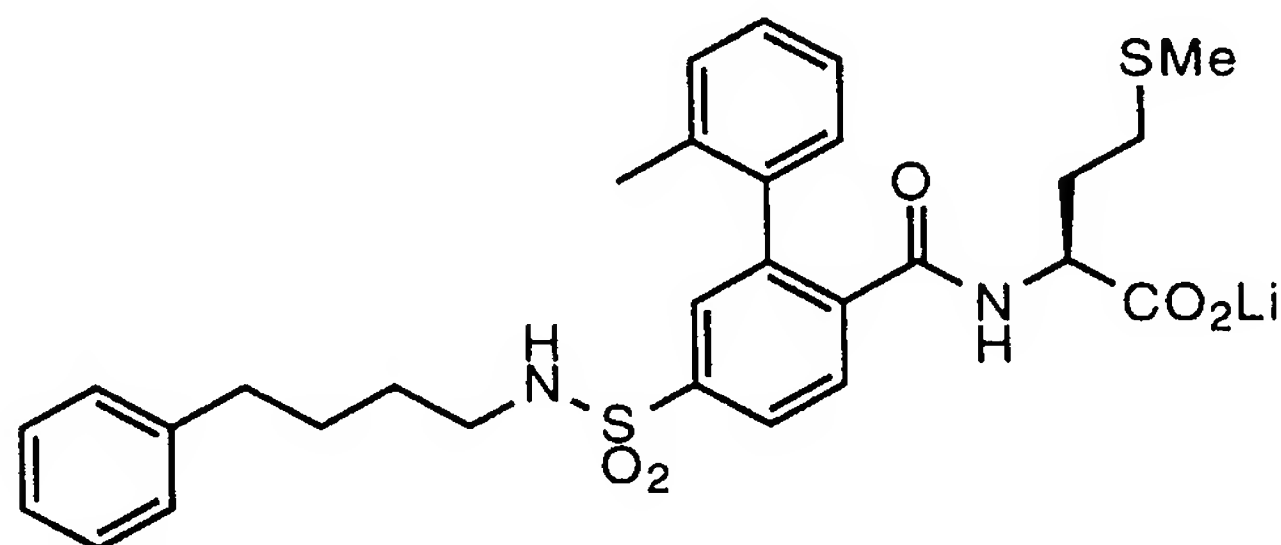
N-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9375 The above compound was prepared from the compound described in Example 1222D according to the method of Example 1205D. MS (APCI) 532 (M+H)<sup>+</sup>.

Example 1222F

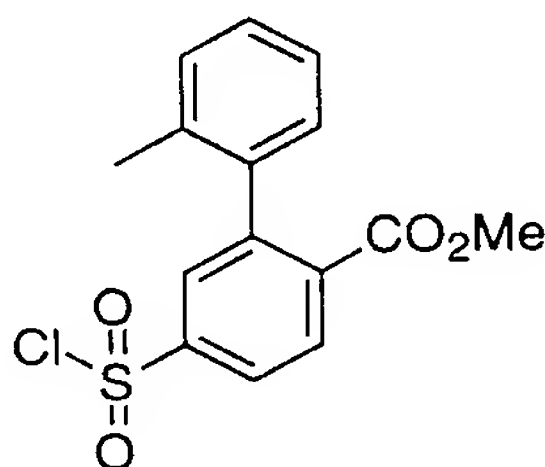
N-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9380 The above compound was prepared from the compound described in Example 1222E according to the method of Example 1178J, except the lithium salt was not made. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 8.15 (d, 1H), 7.46 (d, 1H), 7.31 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80 (m, 2H), 1.60 (m, 4H), 1.40 (m, 8H), 0.85 (t, 6H). MS (ESI) 516 (M-H)<sup>-</sup>. Anal calcd for C<sub>28</sub>H<sub>40</sub>NO<sub>4</sub>PS: 9385 C, 64.97; H, 7.79; N, 2.71. Found: C, 64.87; H, 7.83; N, 2.72.



Example 1278

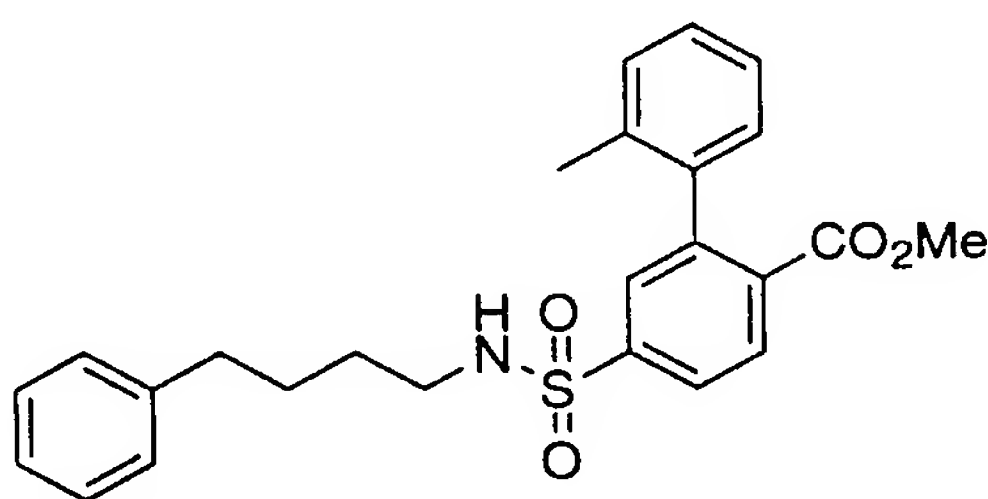
9390

N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine lithium salt.Example 1278A

9395

4-amino-2-(2-methylphenyl)benzoic acid methyl ester (4.5 g, 0.018 mol) in an excess of concentrated (38%) hydrochloric acid (25 ml), was diazotized at 0°C with sodium nitrite (1.45 g, 0.0216 mol). The solution of diazonium chloride was added with stirring to a mixture of sulfur dioxide (40 g), 1,2-dichlorobenzene (10 ml), copper(II) chloride (1.4 g), and potassium chloride (1.4 g) in dioxane (20 ml), and heated to 40-50°C. After the evolution of nitrogen was complete (about 30 min.), water (200 ml) was added and the sulfonyl chloride was extracted with methylene chloride. The organic layer was washed quickly with 10% sodium hydroxide (3\*50 ml), followed by washing with water. After drying over anhydrous magnesium sulfate, the organic solvents were removed under reduced pressure. A brown liquid of the title compound (4.8 g, 82%) was obtained. <sup>1</sup>H NMR: 2.09(3H, s), 3.65(3H, s), 7.0-7.1(1H, d), 7.2-7.4(3H, m), 7.9-8.0(1H, d), 8.1-8.2(2H, m). <sup>13</sup>C NMR: 20.0 (CH<sub>3</sub>), 52.6 (OCH<sub>3</sub>), 125.5, 125.6, 128.4, 129.2, 130.0, 131.0, 135.0, 135.0, 138.6, 144.2, 146.0, 166.0. (DSI/NH<sub>3</sub>)MS: 324 (M+NH<sub>4</sub>)<sup>+</sup>.

9405

Example 1278B

9410

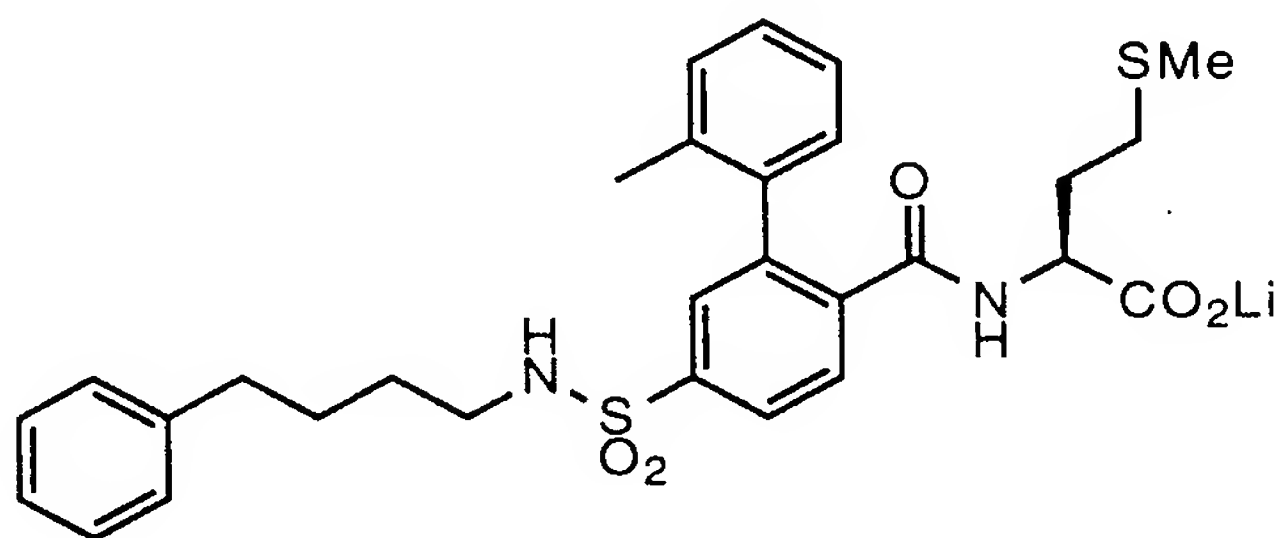
A mixture of 1278B (0.32 g, 1.0 mmol), 4-phenylbutylamine (0.223 g, 1.5 mmol), and 0.2 ml of pyridine in 5 ml of anhydrous methylene chloride was stirred for 12 hours. The reaction mixture was washed by 10% HCl, brine, and dried over anhydrous MgSO<sub>4</sub>. Flash chromatography of the residue eluting with 4:6EtOAc/Hexane afforded 0.205 g of the title compound. NMR(CDCl<sub>3</sub>) 8.00-8.05 (m, 1H); 7.85-7.92 (m, 1H); 7.73 (s, 1H); 7.00-

9415 7.30 (m, 8H); 4.35-4.45 (m, 1H); 3.65 (s, 3H); 2.95-3.08 (t, 2H); 2.55-2.62 (t, 2); 2.08 (s, 3H); 1.4-1.67 (m, 4H). (DSI/NH<sub>3</sub>)MS: 455 (M+NH<sub>4</sub>)<sup>+</sup>.

#### Example 1278C

Prepared according to the procedure of example 1258C from 1278B NMR(CDCl<sub>3</sub>)

9420 8.00-8.10 (m, 1H); 7.88-7.94 (m, 1H); 7.73 (s, 1H); 7.10-7.40 (m, 8H); 5.93-6.00 (m, 1H); 4.52-4.60 (m, 1H); 4.32-4.40 (m, 1H); 3.70 (s, 3H); 2.95-3.08 (t, 2H); 2.55-2.62 (t, 2); 2.0-2.2 (m, 10H); 1.70-2.00 (m, 1H); 1.50-1.70 (m, 4H). (DSI/NH<sub>3</sub>)MS: 569(M+H)<sup>+</sup>; 586 (M+NH<sub>4</sub>)<sup>+</sup>.



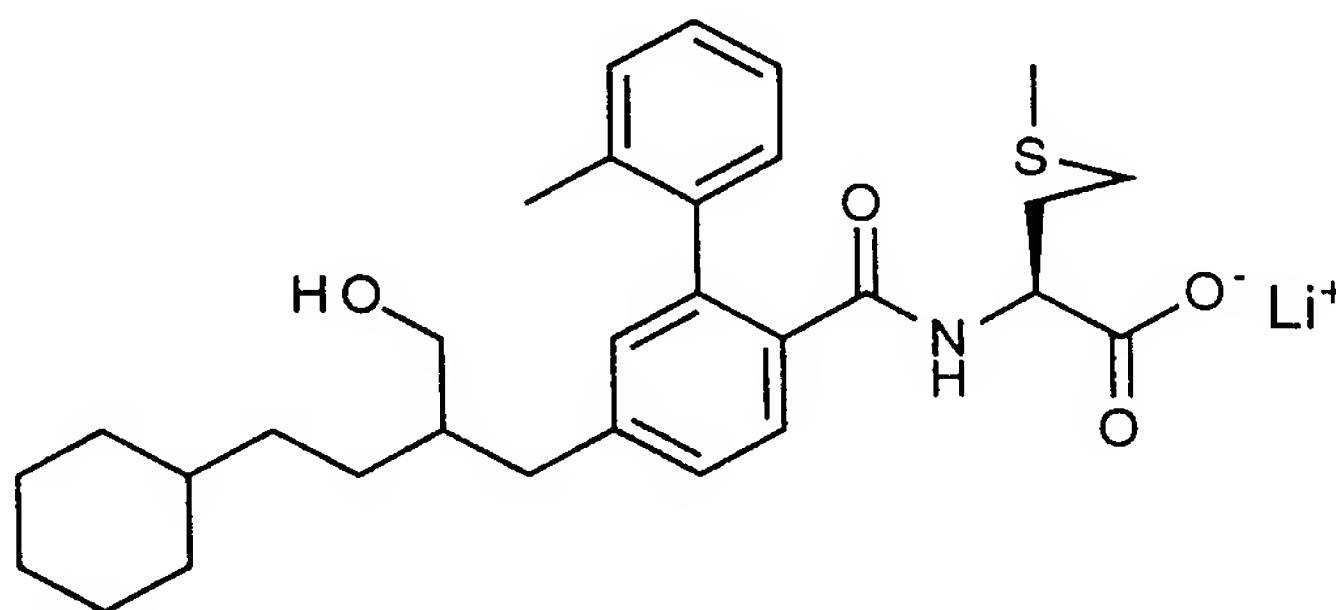
9425

#### Example 1278

N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine lithium salt.

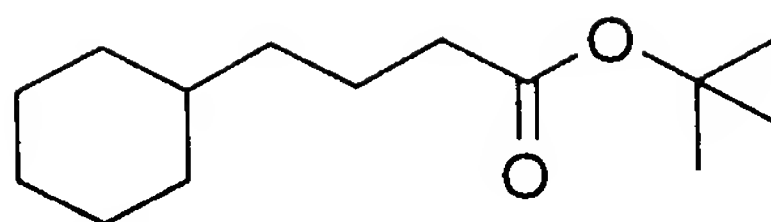
Prepared according to the procedure of example 1178J from 1296C. NMR

9430 <sup>1</sup>H(MeOH-d<sub>4</sub>): 7.8-7.9 (2H, m); 7.7 (1H, s); 7.1-7.3 (13H, m); 4.2-4.3 (1H, m); 2.85-2.95 (2H, m); 2.5-2.6 (2H, m); 1.6-2.3 (14H, m). ESI(-)/MS: 553(M-Li).

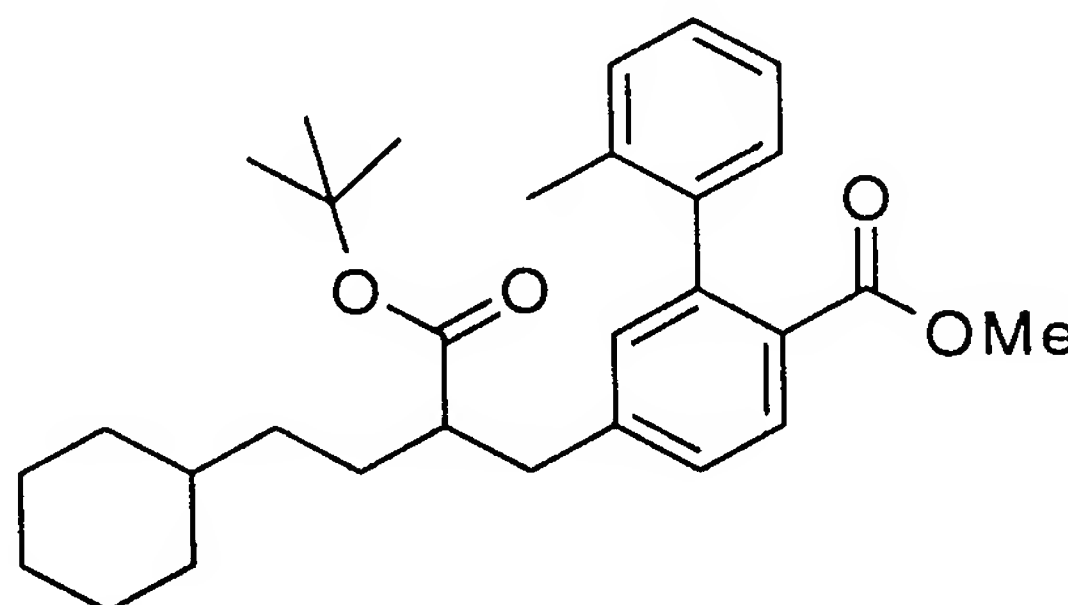


#### Example 1299

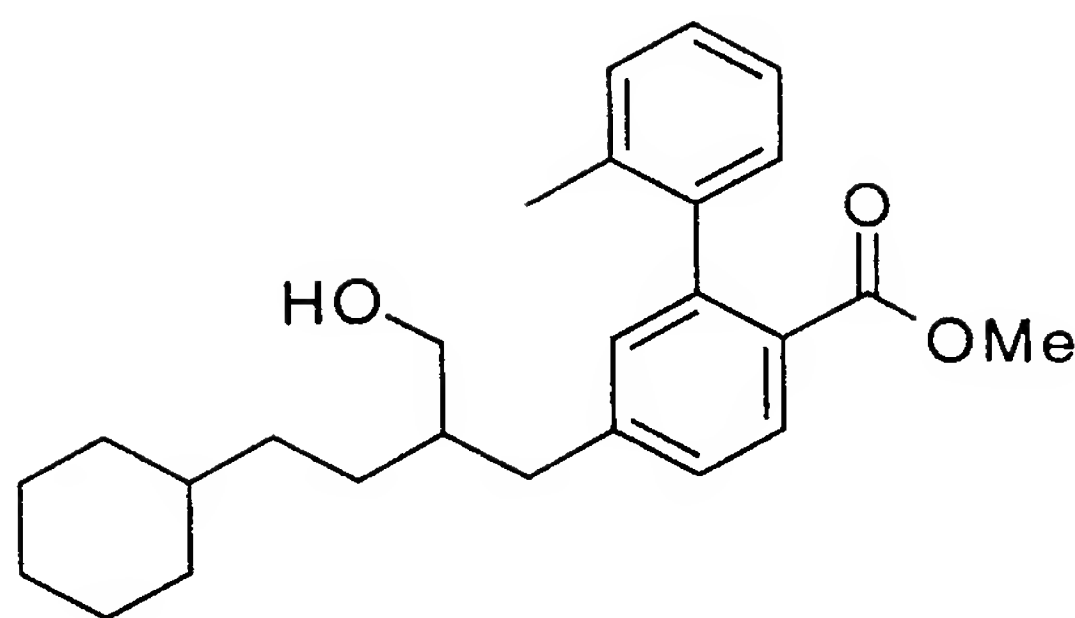
9435 N-[4-(2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

Example 1299Atert-Butyl 4-cyclohexylbutyrate

4-Cyclohexylbutyric acid (1.8 g, 10.6 mmol), isobutylene (25 mL) and concentrated sulfuric acid (0.3 mL) were combined in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) in a pressure bottle. After shaking for 8 days, the pressure bottle was placed in a -78 °C bath and a saturated solution of NaHCO<sub>3</sub> was added and the phases separated. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to afford crude ester as a clear oil (2.3 g). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.81-0.94 (m, 2H), 1.14-1.25 (m, 6H), 1.44 (s, 9H) 1.55-1.74 (m, 7H), 2.18 (t, J=7.5 Hz, 2H); MS (CI/NH<sub>3</sub>) m/z: (M+H)<sup>+</sup> 227.

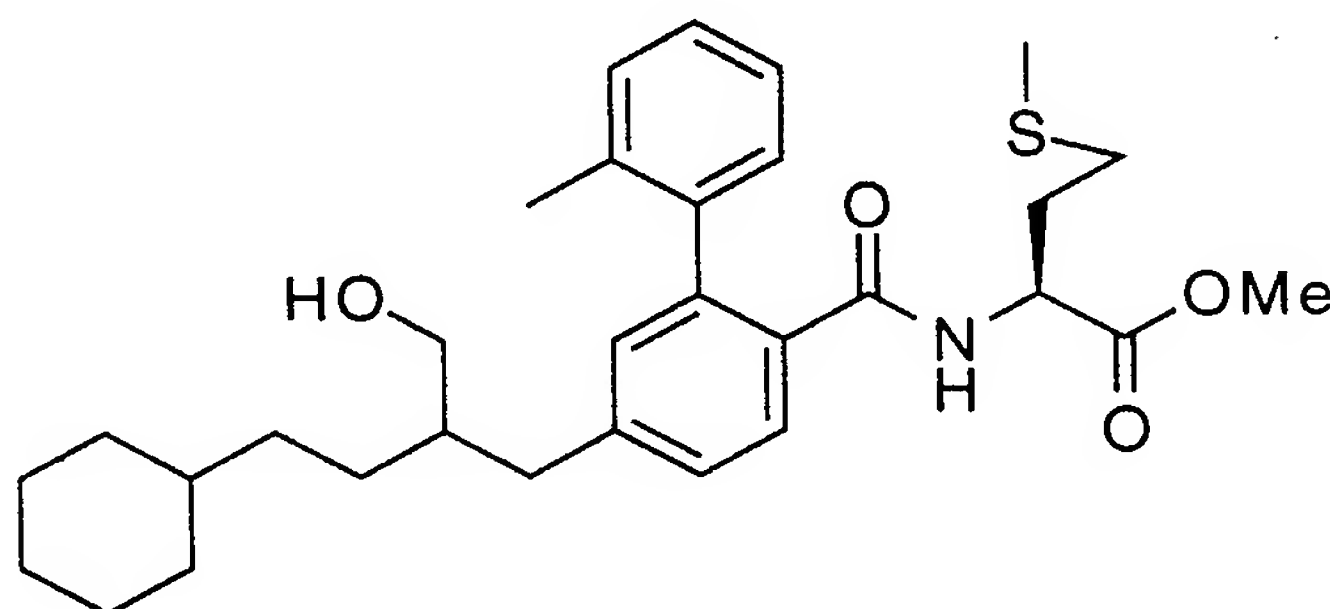
Example 1299B4-[2-(2-Cyclohexylethyl)t-butylpropion-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

A 1.6M solution of n-BuLi in hexanes (1.7 mL, 2.7 mmol) was added to a solution of diisopropylamine (385 µL, 2.7 mmol) at ambient temperature. After 10 minutes of stirring, the solution was cooled to -78 °C and the product from Example 1299A (600 mg, 2.6 mmol) in THF (2.5 mL) was added to the reaction mixture. After stirring for 15 min, the cold bath was removed. After 30 min of stirring, the mixture was re-cooled to -78 °C and the product from Example 1308E (1.0 g, 2.7 mmol) in THF (2.0 mL) was added to the reaction mixture. The mixture was allowed to gradually warm to ambient temperature and stir over night. A solution of 2N HCl was added and the mixture extracted with EtOAc (2X). The organic phases were combined, dried (MgSO<sub>4</sub>) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:40) to afford a clear oil (572 mg, 47%). MS (CI/NH<sub>3</sub>) m/z: (M+H)<sup>+</sup> 465.

Example 1299C4-[2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

Trifluoroacetic acid (3 mL) was added to a solution of the product from Example 1299B (448 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at ambient temperature. After stirring for 90 min, solvent was evaporated to dryness. MS (CI/NH<sub>3</sub>) m/z: (M+H)<sup>+</sup> 409.

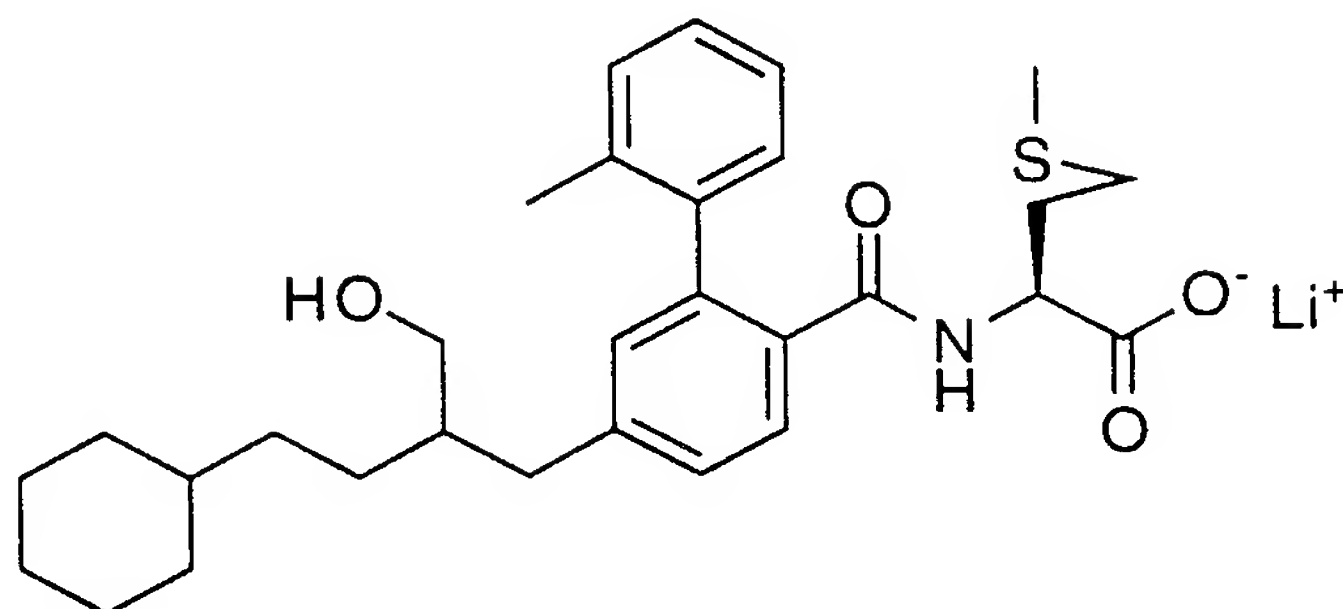
A 1.0M solution of borane THF complex (2.1 mL, 2.1 mmol) was added to a solution of the crude product described above in THF (3 mL) at ambient temperature. After stirring for 6 hours, a 2N solution of HCl was added to the reaction mixture. After 90 min of stirring, the mixture was extracted with EtOAc (2X). The organic phases were combined, dried (MgSO<sub>4</sub>) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (256 mg, 68%). MS (CI/NH<sub>3</sub>) m/z: (M+H)<sup>+</sup> 395.

Example 1299DN-[4-[2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The product from Example 1299C (97 mg, 0.25 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (55 mg, 0.28 mmol), Hobt (30 mg, 0.22 mmol), (L)-methionine methyl ester hydrochloride (48 mg, 0.24 mmol) and NMM (40  $\mu$ L, 0.36 mmol) in DMF (1 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed



(silica gel; EtOAc/hexanes, 1:2) to afford the title compound as a clear oil (66 mg, 63%). MS (CI/NH<sub>3</sub>) m/z: (M+H)<sup>+</sup> 526.



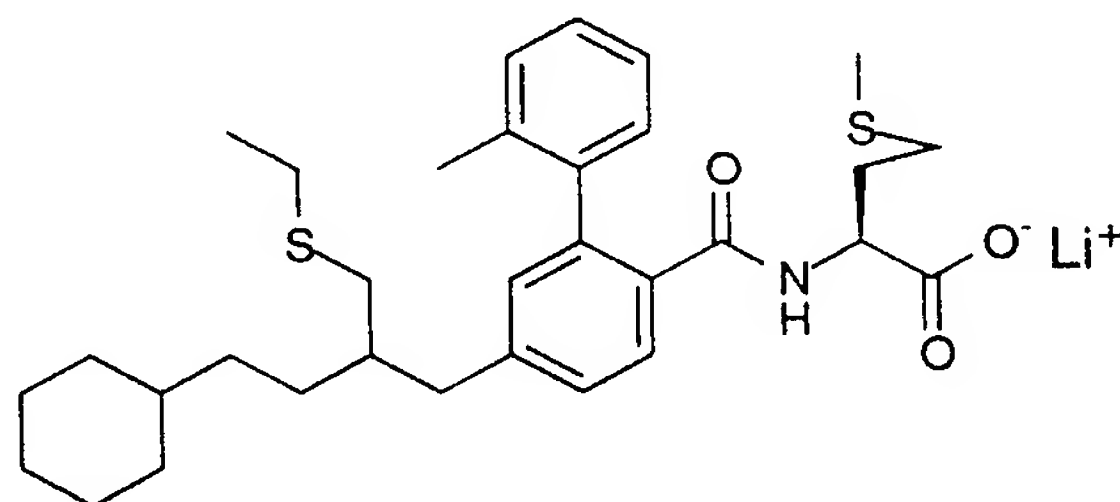
9490

#### Example 1299E

#### N-[4-(2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The product from Example 1299D (60 mg, 0.11 mmol) was allowed to react with lithium hydroxide monohydrate (5 mg, 0.12 mmol) in a manner similar to that described in Example 608E to afford the title compound. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.72-0.88 (m, 2H), 1.03-1.30 (m, 8H), 1.52-1.70 (m, 9H), 1.88-2.03 (m, 6H), 2.15 (m, 1H), 2.47 (m, partially buried under DMSO peak 1H), 2.70 (m, 1H), 3.32 (d, partially buried under water peak 2H), 4.42 (m, 1H), 6.90 (d, J=6 Hz, 1H), 6.94 (s, 1H), 7.10-7.25 (m, 4H), 7.46 (d, J=8 Hz, 1H); MS (APCI(-)) m/z: (M-H)<sup>-</sup> 510; Anal. Calcd for C<sub>30</sub>H<sub>40</sub>LiNO<sub>4</sub>S•2.1 H<sub>2</sub>O: C, 64.87; H, 8.02; N, 2.52. Found: C, 64.89; H, 7.37; N, 2.37.

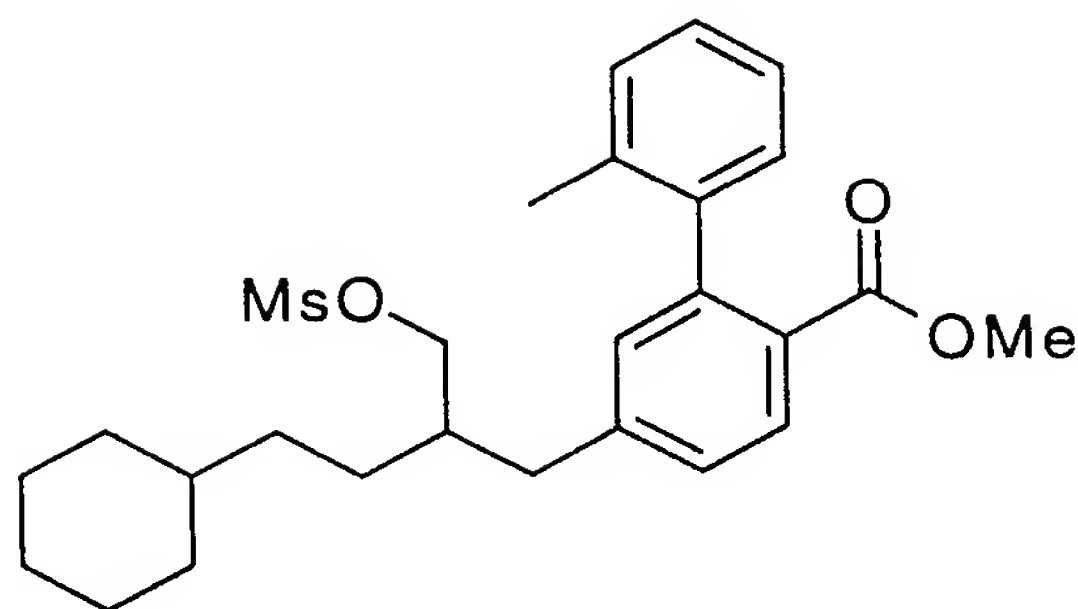
9500



9505

#### Example 1300

#### N-[4-(2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

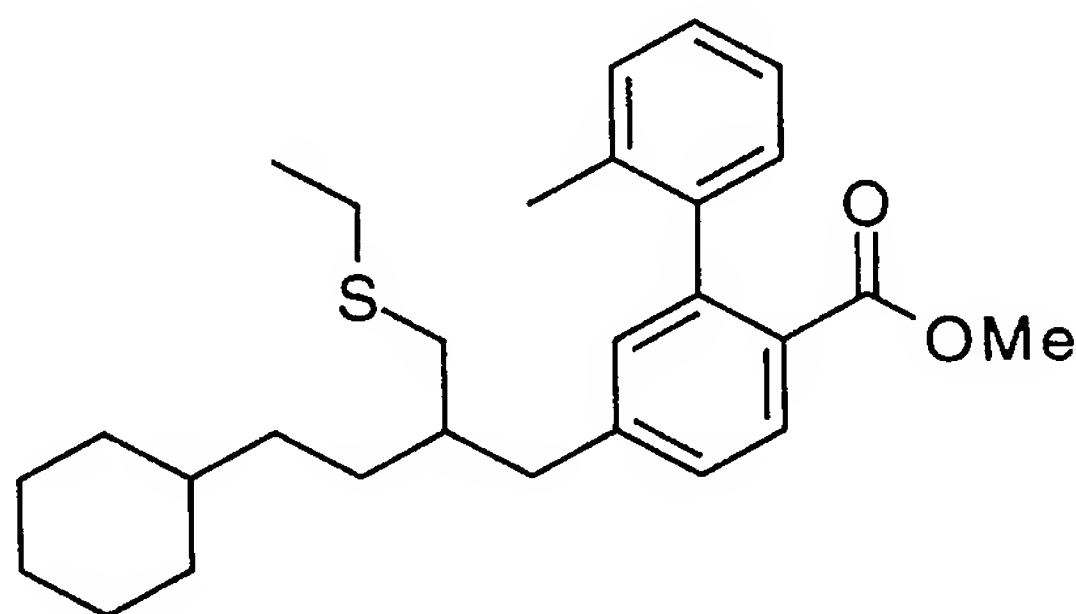


9510

Example 1300A4-[2-(2-Cyclohexylethyl)-1-methylsulfonyloxyprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

9515 Methanesulfonyl chloride (33  $\mu$ L) was added to a solution of the product from Example 1299C (149 mg, 0.38 mmol) and triethylamine (60  $\mu$ L, 0.42 mmol) in THF (1 mL) at 0  $^{\circ}$ C. The reaction mixture was allowed to warm to ambient temperature and stir for 3 hours. A solution of 2N HCl was added to the mixture which was then extracted with EtOAc. The organic phase was separated, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (111 mg, 62%).

9520  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.75-0.90 (m, 2H), 1.07-1.27 (m, 6H), 1.35-1.43 (m, 2H), 1.60-1.66 (m, 5H), 2.04 (m, 1H), 2.05 (s, 3H), 2.66-2.81 (m, 2H), 2.96 (s, 3H), 3.61 (s, 3H), 4.10 (d,  $J=5$  Hz, 2H), 7.04-7.07 (m, 2H), 7.18-7.29 (m, 4H), 7.92 (d,  $J=8$  Hz, 1H); MS ( $\text{CI}/\text{NH}_3$ )  $m/z$ : ( $\text{M}+\text{H}$ ) $^+$  473.

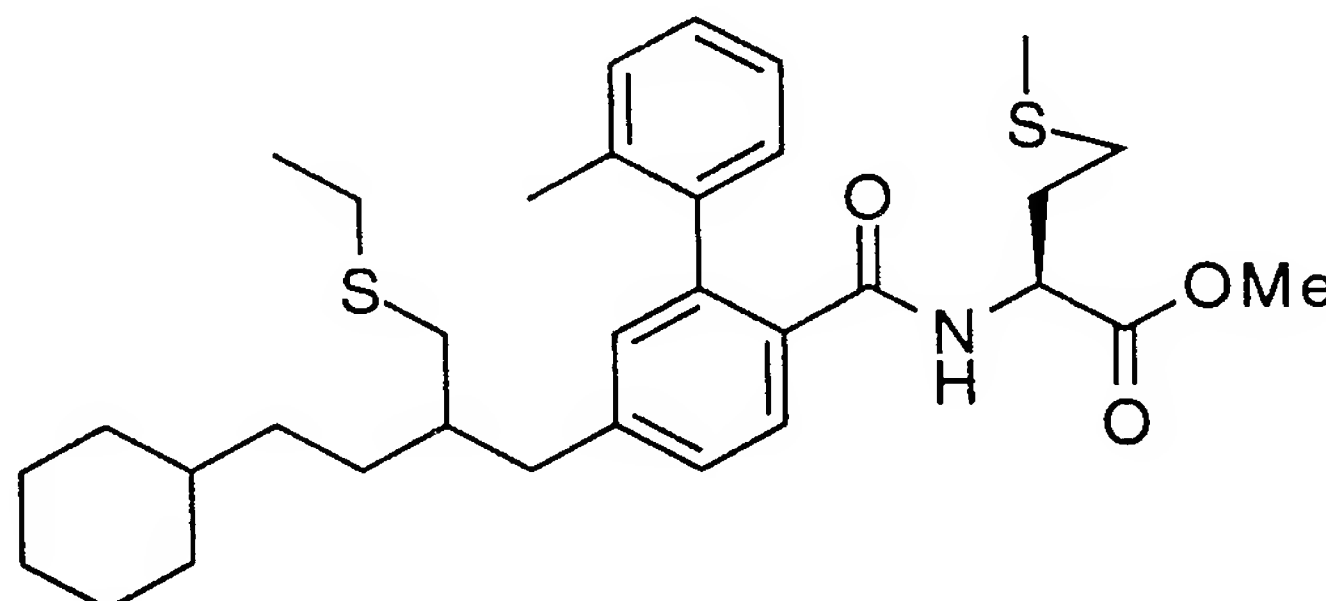


9525

Example 1300B4-[2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

9530 Ethanethiol (50  $\mu$ L, 0.66 mmol) was added to a 60% dispersion in mineral oil NaH (27 mg, 0.68 mmol) slurry in THF (0.7 mL) at ambient temperature. After stirring for 40 min, the product from Example 1300A (105 mg, 0.22 mmol) in THF (0.7 mL) was added to the reaction mixture followed by heating at reflux for 90 min. The mixture was allowed to cool to ambient temperature and a solution of 2N HCl was added to the reaction vessel. The

9535 mixture was extracted with EtOAc (2X). The organic phases were combined, dried (MgSO<sub>4</sub>) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:10) to afford a clear oil (83 mg, 86%). MS (CI/NH<sub>3</sub>) m/z: 439 (M+H)<sup>+</sup>.

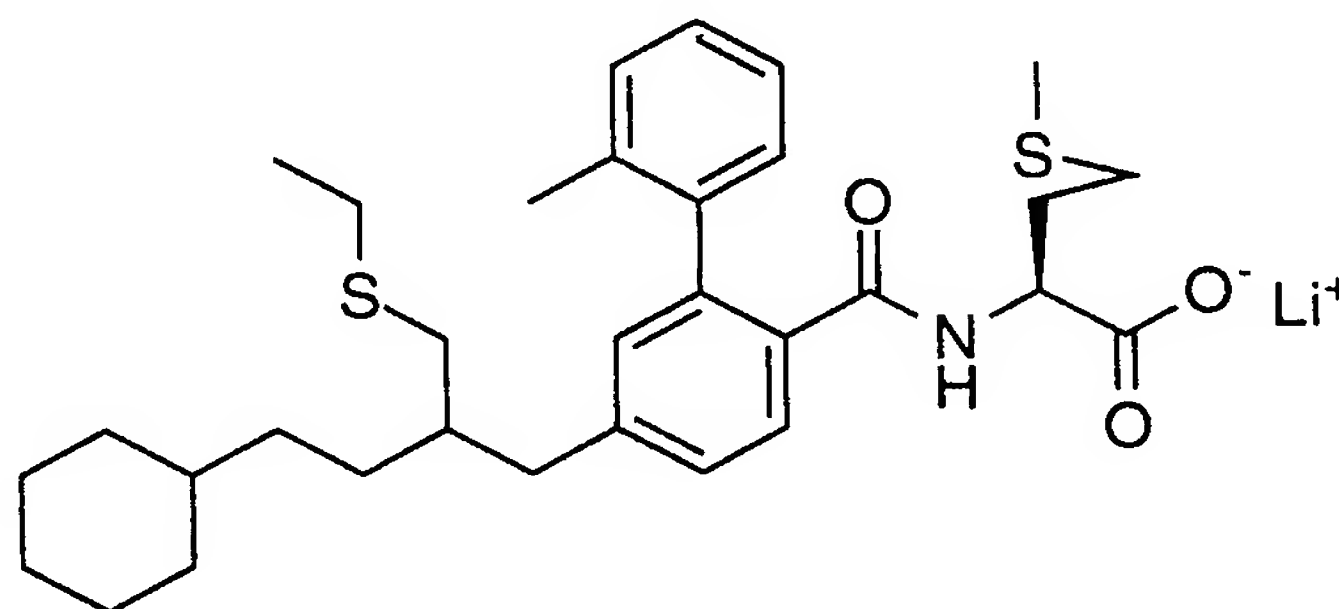


9540

Example 1300C

N-[4-[2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

9545 The product from Example 1300B (78 mg, 0.18 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (48 mg, 0.25 mmol), Hobt (27 mg, 0.20 mmol), (L)-methionine methyl ester hydrochloride (43 mg, 0.22 mmol) and NMM (35  $\mu$ L, 0.32 mmol) in DMF (1.0 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford the title compound as a clear oil (46.5 mg, 45%).



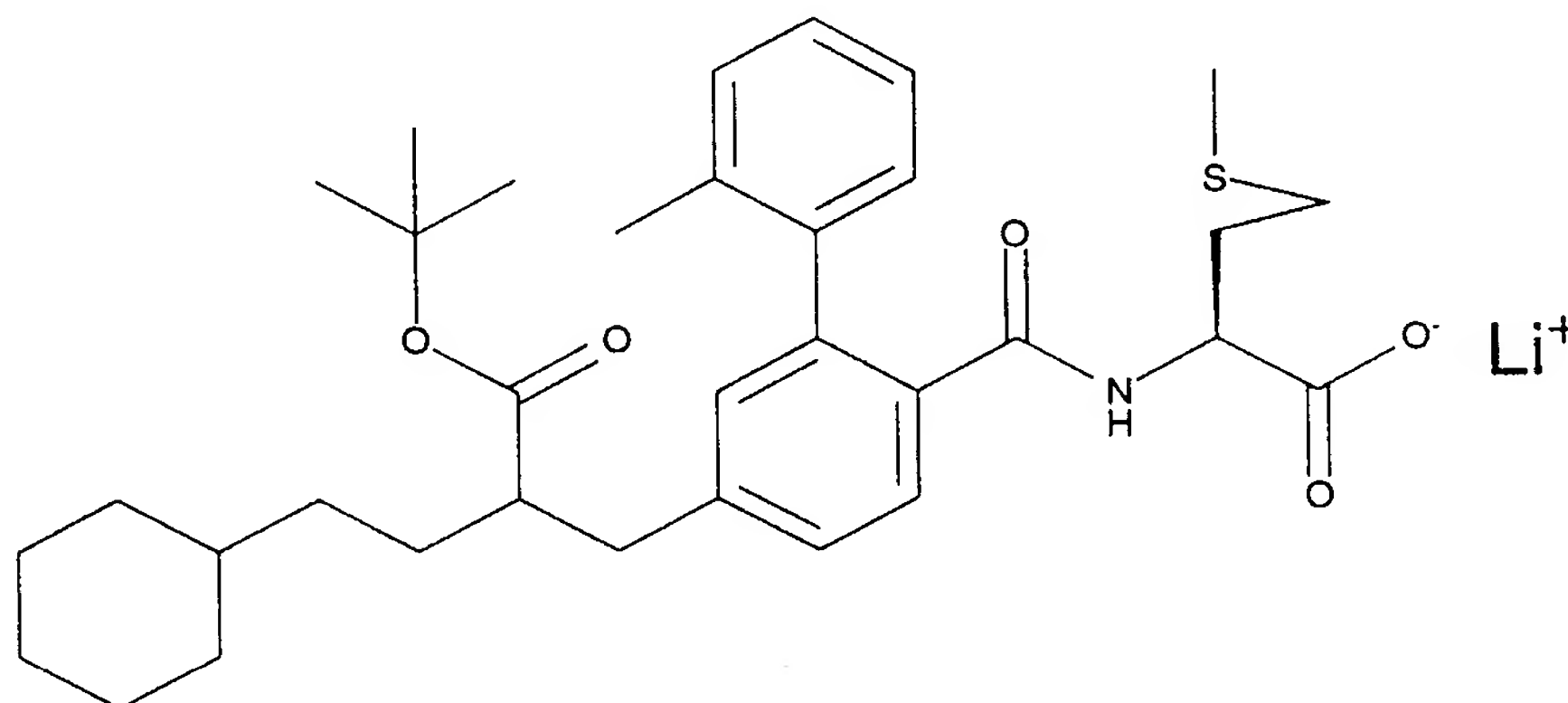
9550

Example 1300D

N-[4-(2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

9555 The product from Example 1300C (46.5 mg, 0.08 mmol) was allowed to react with lithium hydroxide monohydrate (4 mg, 0.08 mmol) in a manner similar to that described in Example 608E to afford the title compound. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  0.75-0.88 (m, 2H), 1.08-1.38 (m, 10H), 1.53-2.01 (m, 14H), 2.15 (m, 1H), 2.39-2.49 (m, 4H),

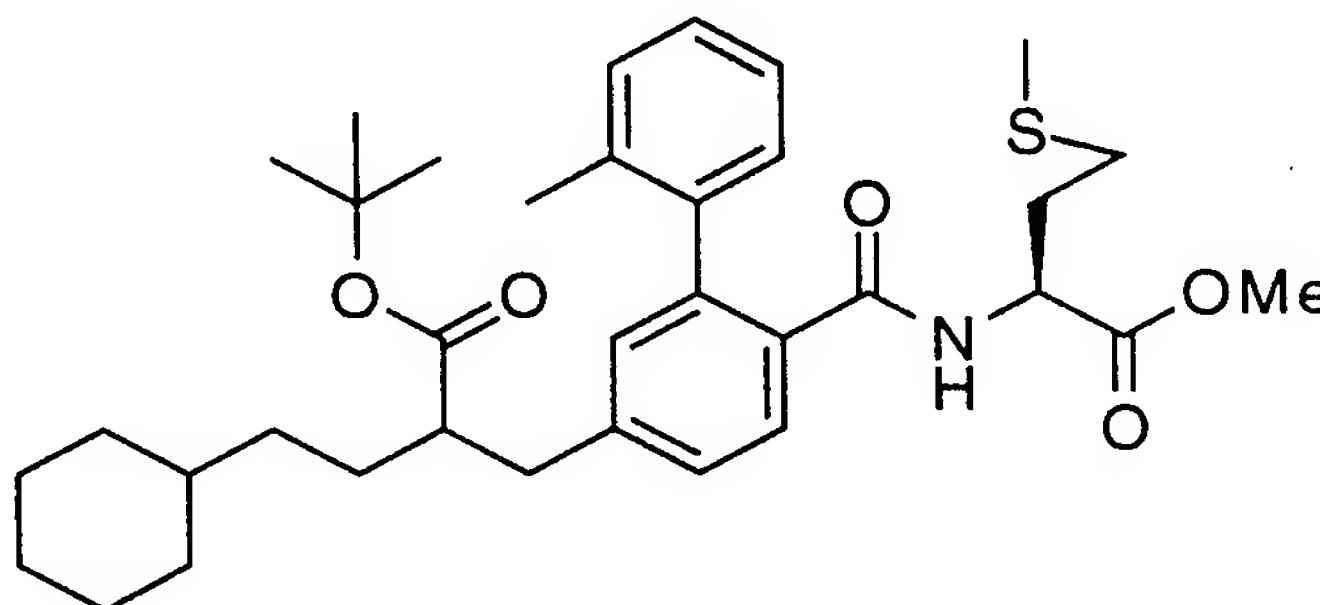
2.57-2.75 (m, 2H), 3.32 (d, partially buried under water peak 2H), 3.66 (m, 1H), 6.86 (d, J=6 Hz, 1H), 6.95 (m, 1H), 7.12-7.26 (m, 4H), 7.47 (d, J=8 Hz, 1H); MS (APCI(-)) m/z: (M-H)<sup>-</sup> 554; Anal. Calcd for C<sub>32</sub>H<sub>44</sub>LiNO<sub>3</sub>S<sub>2</sub>•1.75 H<sub>2</sub>O: C, 64.78; H, 8.07; N, 2.36. Found: C, 64.75; H, 7.40; N, 2.20.



9565

Example 1301

N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine  
Lithium Salt

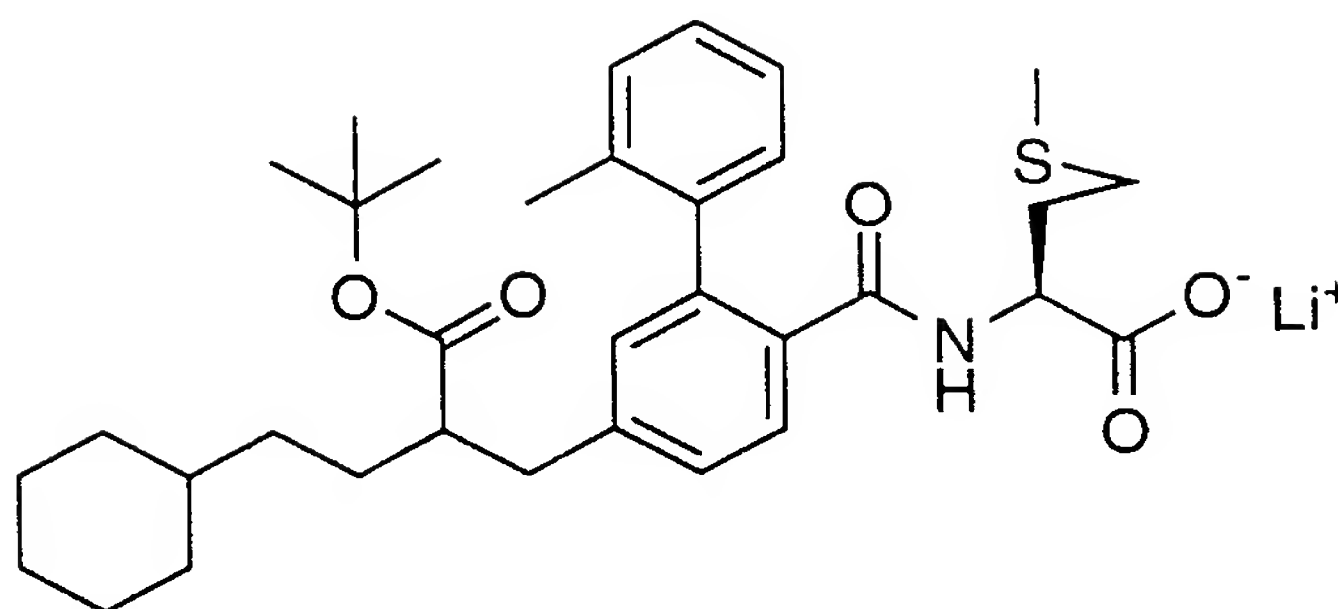


9570

Example 1301A

N-[4-(2-(2-Cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine  
methyl ester

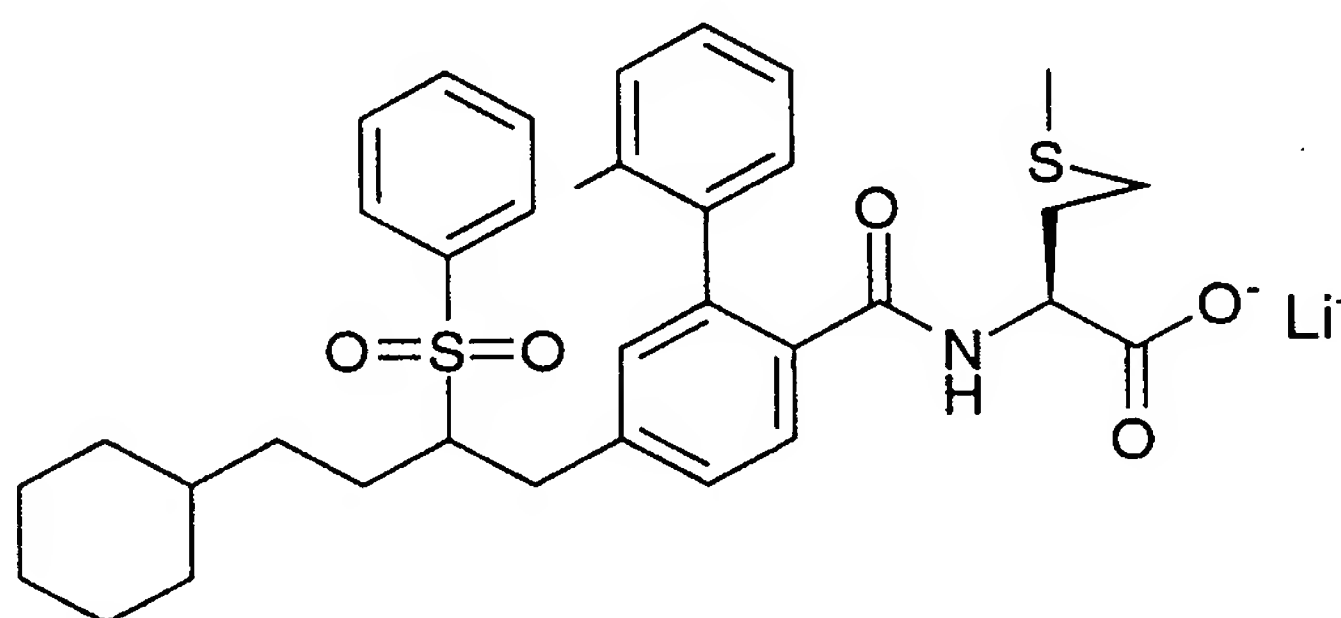
The product from Example 1299B (99 mg, 0.21 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (56 mg, 0.29 mmol), Hobt (31 mg, 0.23 mmol), (L)-methionine methyl ester hydrochloride (50 mg, 0.25 mmol) and NMM (42  $\mu$ L, 0.38 mmol) in DMF (1.0 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed (silica gel; EtOAc/hexanes) to afford the title compound as a clear oil (62 mg, 49.5%).



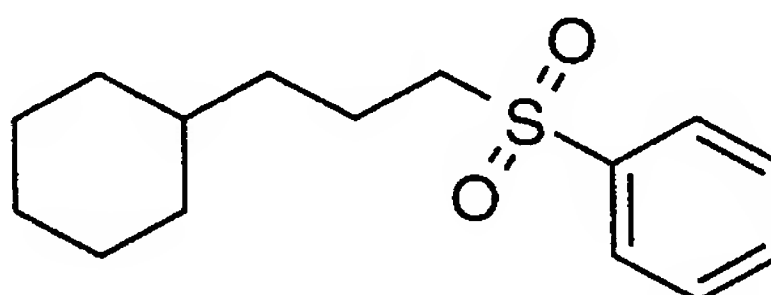
9580

Example 1301BN-[4-(2-(2-Cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine  
Lithium Salt

The product from Example 1301A (61 mg, 0.10 mmol) was allowed to react with  
 9585 lithium hydroxide monohydrate (4.5 mg, 0.08 mmol) in a manner similar to that described  
 in Example 608E to afford the title compound. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 0.75-  
 0.90 (m, 2H), 1.05-1.35 (m, 15H), 1.45-2.03 (m, 17H), 2.15 (m, 1H), 2.75-2.80 (m,  
 2H), 3.65 (m, 1H), 6.86-7.00 (m, 2H), 7.07-7.25 (m, 4H), 7.46 (d, J=8 Hz, 1H); MS  
 (APCI(-)) m/z: (M-H)<sup>-</sup> 580; Anal. Calcd for C<sub>34</sub>H<sub>46</sub>LiNO<sub>5</sub>S•1.70 H<sub>2</sub>O: C, 66.04; H,  
 9590 8.05; N, 2.26. Found: C, 66.01; H, 7.54; N, 2.27.

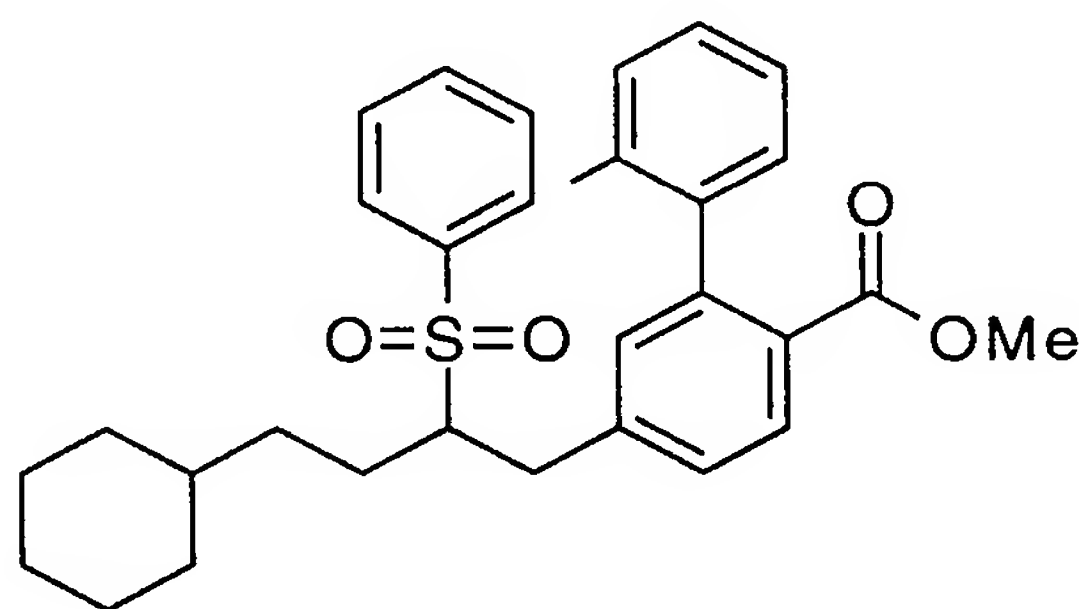
Example 1302N-[4-(4-Cyclohexyl-2-phenylsulfonyl)but-1-yl]-2-(2-methylphenyl)benzoyl]methionine  
Lithium Salt

9595

Example 1302A3-Cyclohexylpropyl phenyl sulfone

9600

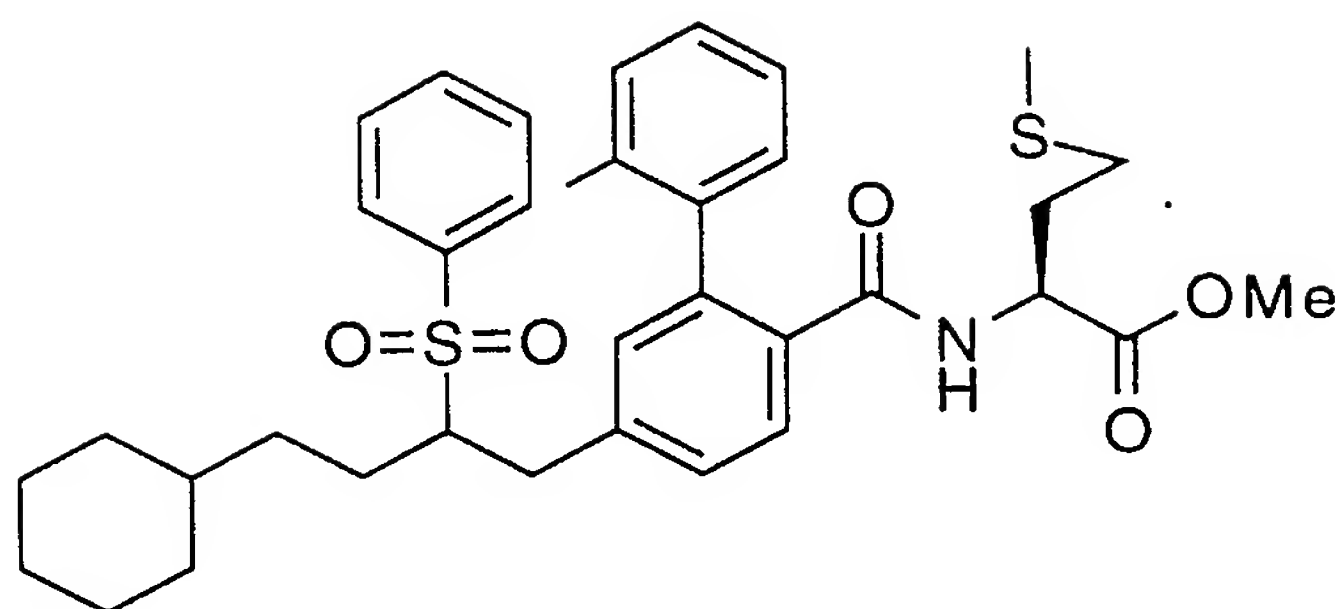
A solution of 2.5M nBuLi in hexanes (1.9 mL, 4.7 mmol) was added to a solution of diisopropylamine (660  $\mu$ L, 4.7 mmol) in THF (9.0 mL) at ambient temperature. After 10 min, the mixture was cooled to -78  $^{\circ}$ C and methyl phenyl sulfone (700 mg, 4.5 mmol) was added to the reaction vessel. The cold bath was removed and after stirring for 30 min, 1-bromo-2-cyclohexylethane (1.3 g, 6.7 mmol) was added to the reaction mixture. The mixture was allowed to warm to ambient temperature and stir for 18 hours. A solution of 2N HCl was added to the reaction mixture followed by extraction with EtOAc (2X). The organic phases were combined, dried (MgSO<sub>4</sub>) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (620 mg, 52%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, MHz)  $\delta$  0.75-0.91 (m, 2H), 1.07-1.26 (m, 6H), 1.58-1.76 (m, 7H), 3.06 (t, J=8 Hz, 2H), 7.55-7.70 (m, 3H), 7.92 (m, 2H); MS (CI/NH<sub>3</sub>) m/z: (M+NH<sub>4</sub>)<sup>+</sup> 284.



#### Example 1302B

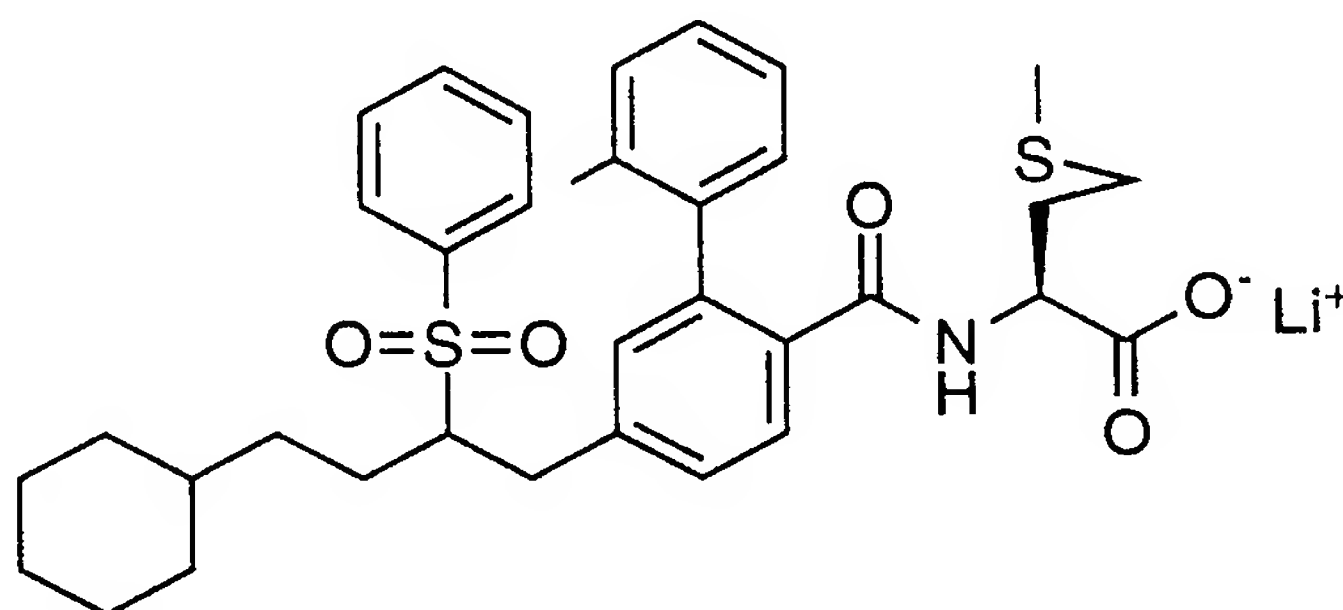
N-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The product from Example 1302A (200 mg, 0.75 mmol) was allowed to react with diisopropylamine (110  $\mu$ L, 0.79 mmol), 1.6M nBuLi in hexanes (495  $\mu$ L, 0.79 mmol) and the product from Example 1308E (302 mg, 0.82 mmol) in a manner similar to that described under Example 1302A. The crude residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (179 mg, 47%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, MHz)  $\delta$  0.60-0.75 (m, 2H), 0.90-1.15 (m, 6H), 1.43 (m, 1H), 1.50-1.64 (m, 5H), 1.84 (m, 1H), 2.02 (s, 3H), 2.78 (m, 1H), 3.22 (m, 1H), 3.38 (m, 1H), 3.60 (s, 3H), 6.95-7.02 (m, 2H), 7.14-7.29 (m, 4H), 7.53-7.88 (m, 3H), 7.86-7.93 (m, 3H); MS (CI/NH<sub>3</sub>) m/z: (M+NH<sub>4</sub>)<sup>+</sup> 522.

Example 1302CN-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9630 The product from Example 1302B (168 mg, 0.33 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (90 mg, 0.46 mmol), Hobt (50 mg, 0.36 mmol), (L)-methionine methyl ester hydrochloride (80 mg, 0.39 mmol) and NMM (65  $\mu$ L, 0.39 mmol) in DMF (1.3 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed

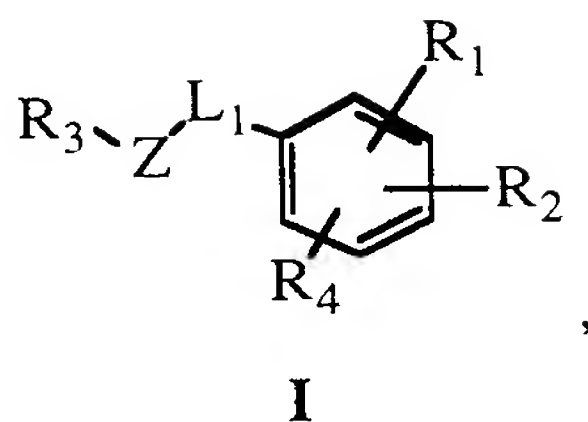
9635 (silica gel; EtOAc/hexanes, 1:4) to afford the title compound as a clear oil (117 mg, 56%).

Example 1302DN-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

9640 The product from Example 1302C (107 mg, 0.17 mmol) was allowed to react with lithium hydroxide monohydrate (8 mg, 0.18 mmol) in a manner similar to that described in Example 608E to afford the title compound.  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  0.54-0.70 (m, 2H), 0.85-1.10 (m, 6H), 1.30-2.04 (m, 16H), 2.14 (m, 1H), 2.80 (m, 1H), 3.16 (m, 1H), 3.60-3.73 (m, 2H), 6.85-7.26 (m, 6H), 7.43 (d,  $J=8$  Hz, 1H), 7.62-7.68 (m, 2H), 7.75 (m, 1H), 7.93 (d,  $J=7$  Hz, 2H); MS (APCI(-))  $m/z$ : (M-H) $^-$  620; Anal. Calcd for  $\text{C}_{35}\text{H}_{42}\text{LiNO}_5\text{S}_2 \cdot 3.20 \text{ H}_2\text{O}$ : C, 61.33; H, 7.12; N, 2.04. Found: C, 61.31; H, 6.63; N, 1.70

WHAT IS CLAIMED IS:

1. A compound having Formula I



or a pharmaceutically acceptable salt thereof, wherein  
**R<sub>1</sub>** is selected from the group consisting of

- 10
- (1) hydrogen,
  - (2) alkenyl,
  - (3) alkynyl,
  - (4) alkoxy,
  - (5) haloalkyl,
  - (6) halogen,
  - 15 (7) loweralkyl,
  - (8) thioalkoxy,
  - (9) aryl-L<sub>2</sub>- wherein aryl is selected from the group consisting of
    - (a) phenyl,
    - (b) naphthyl,
    - 20 (c) dihydronaphthyl,
    - (d) tetrahydronaphthyl,
    - (e) indanyl, and
    - (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,  
 25 or Z wherein X, Y, and Z are independently selected from the  
 group consisting of  
 alkenyl,  
 alkynyl,  
 alkoxy,  
 30 aryl,  
 carboxy,  
 cyano,  
 halogen,



haloalkyl,  
hydroxy,  
hydroxyalkyl,  
loweralkyl,  
5 nitro,  
N-protected amino, and  
-NRR' wherein R and R' are independently selected  
from the group consisting of  
hydrogen and  
10 loweralkyl,  
oxo (=O), and  
thioalkoxy and

L<sub>2</sub> is absent or is selected from the group consisting of

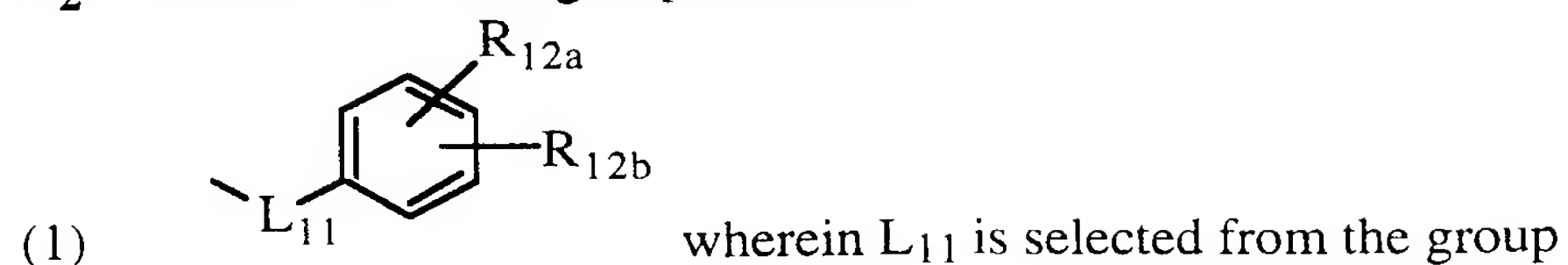
-CH<sub>2</sub>-,  
15 -CH<sub>2</sub>CH<sub>2</sub>-,  
-CH(CH<sub>3</sub>)-,  
-O-,  
-C(O)-,  
-S(O)<sub>q</sub> wherein q is 0, 1 or 2, and  
20 -N(R)-, and

(10) heterocycle-L<sub>2</sub>- wherein L<sub>2</sub> is as defined above and the heterocycle is  
unsubstituted or substituted with 1, 2, 3 or 4 substituents  
independently selected from the group consisting of

- (a) loweralkyl,
- 25 (b) hydroxy,
- (c) hydroxyalkyl,
- (d) halogen
- (e) cyano,
- (f) nitro,
- 30 (g) oxo (=O),
- (h) -NRR',
- (i) N-protected amino,
- (j) alkoxy,
- (k) thioalkoxy,
- 35 (l) haloalkyl,
- (m) carboxy, and

(n) aryl;

$R_2$  is selected from the group consisting of



consisting of

- (a) a covalent bond,
- (b)  $-C(W)N(R)-$  wherein R is defined previously and W is selected from the group consisting of O and S,
- (c)  $-C(O)-$ ,
- (d)  $-N(R)C(W)-$ ,
- (e)  $-CH_2O-$ ,
- (f)  $-C(O)O-$ , and
- (g)  $-CH_2N(R)-$ ,

$R_{12a}$  is selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl, and
- (c)  $-C(O)OR_{13}$  wherein  $R_{13}$  is selected from the group consisting of hydrogen and a carboxy-protecting group, and

$R_{12b}$  is selected from the group consisting of

- (a) hydrogen and
  - (b) loweralkyl,
- with the proviso that  $R_{12a}$  and  $R_{12b}$  are not both hydrogen,

(2)  $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$  wherein  $L_{11}$  is defined previously,

$R_v$  is selected from the group consisting of

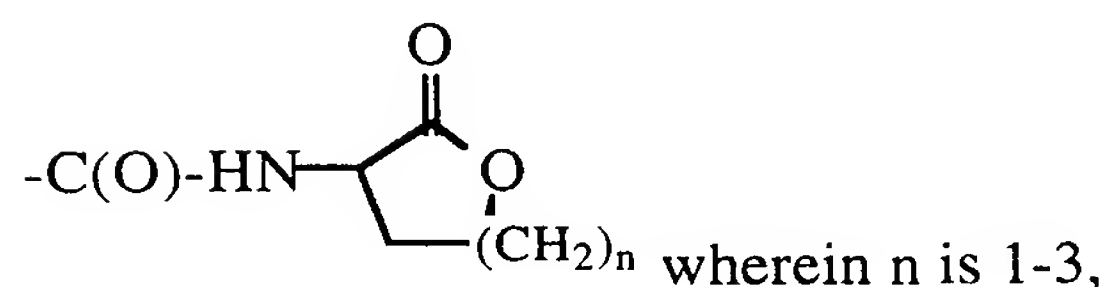
- (a) hydrogen and
  - (b) loweralkyl,
- $R_{15}$  is selected from the group consisting of
- (a) hydrogen,
  - (b) alkanoyloxyalkyl,
  - (c) loweralkyl, and
  - (b) a carboxy-protecting group, and

$R_{14}$  is selected from the group consisting of

- 5 (a) alkoxyalkyl,  
 (b) alkoxyarylalkyl,  
 (c) alkoxycarbonylalkyl,  
 (d) alkylsulfinylalkyl,  
 (e) alkylsulfonylalkyl,  
 (f) alkynyl,  
 (g) aminoalkyl,  
 (h) aminocarbonylalkyl,  
 10 (i) aminothiocabonylalkyl,  
 (j) aryl,  
 (k) arylalkyl,  
 (l) carboxyalkyl,  
 (m) cyanoalkyl,  
 15 (n) cycloalkyl,  
 (o) cycloalkylalkoxyalkyl,  
 (p) cycloalkylalkyl,  
 (q) (heterocyclic)alkyl,  
 (r) hydroxyalkyl,  
 20 (s) hydroxyarylalkyl,  
 (t) loweralkyl,  
 (u) sulfhydrylalkyl,  
 (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is  
 unsubstituted or substituted with 1, 2, 3, or 4  
 25 substituents selected from the group consisting of  
 halogen,  
 (w) thioalkoxyalkylamino, and  
 (x) thiocycloalkyloxyalkyl,

30

(3)



(4)

$-C(O)NH-CH(R_{14})-C(O)NH SO_2 R_{16}$  wherein  $R_{14}$  is defined previously  
 and  $R_{16}$  is selected from the group consisting of  
 (a) loweralkyl,

- (b) haloalkyl,
- (c) aryl wherein the aryl is unsubstituted or substituted with  
1, 2, 3, 4, or 5 substituents independently  
selected from the group consisting of  
loweralkyl,  
hydroxy,  
hydroxyalkyl,  
halogen,  
cyano,  
nitro,  
oxo (=O),  
-NRR'  
N-protected amino,  
alkoxy,  
thioalkoxy,  
haloalkyl,  
carboxy, and  
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or  
substituted with substituents independently  
selected from the group consisting of  
loweralkyl,  
hydroxy,  
hydroxyalkyl,  
halogen,  
cyano,  
nitro,  
oxo (=O),  
-NRR',  
N-protected amino,  
alkoxy,  
thioalkoxy,  
haloalkyl,  
carboxy, and  
aryl;

(5)  $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{tetrazolyl}$  wherein the tetrazole ring is unsubstituted or substituted with loweralkyl or haloalkyl,

(6)  $-\text{L}_{11}-\text{heterocycle}$ ,

(7)  $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(\text{O})\text{NR}_{17}\text{R}_{18}$  wherein  $\text{R}_{14}$  is defined previously and  $\text{R}_{17}$  and  $\text{R}_{18}$  are independently selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

(8)  $-\text{C}(\text{O})\text{OR}_{15}$ , and

(9)  $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{heterocycle}$  wherein  $\text{R}_{14}$  is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;

$\text{L}_1$  is absent or is selected from the group consisting of

(1)  $-\text{L}_4-\text{N}(\text{R}_5)-\text{L}_5-$  wherein  $\text{L}_4$  is absent or selected from the group consisting of

- (a)  $\text{C}_1$ -to- $\text{C}_{10}$ -alkylene and
- (b)  $\text{C}_2$ -to- $\text{C}_{16}$ -alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

alkenyl,  
alkenyloxy,  
alkenyloxyalkyl,  
alkenyl $[\text{S}(\text{O})_q]$ alkyl,  
alkoxy,

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents,

with the proviso that no two hydroxyls are attached to the

same carbon,  
alkoxycarbonyl wherein the alkoxycarbonyl is  
unsubstituted or substituted with 1, 2, or 3  
substituents independently selected from the  
group consisting of  
5 halogen and  
cycloalkyl,  
alkylsilyloxy,  
alkyl[S(O)<sub>q</sub>],  
10 alkyl[S(O)<sub>q</sub>]alkyl,  
aryl wherein the aryl is unsubstituted or substituted with  
1, 2, 3, 4, or 5 substituents independently  
selected from the group consisting of  
alkoxy wherein the alkoxy is unsubstituted or  
15 substituted with substituents selected  
from the group consisting of cycloalkyl,  
aryl,  
arylalkyl,  
aryloxy wherein the aryloxy is unsubstituted or  
20 substituted with 1, 2, 3, 4, or 5  
substituents independently selected from  
the group consisting of,  
halogen,  
nitro, and  
25 -NRR',  
cycloalkyl,  
halogen,  
loweralkyl,  
hydroxyl,  
30 nitro,  
-NRR', and  
-SO<sub>2</sub>NRR',  
arylalkoxy wherein the arylalkoxy is unsubstituted or  
substituted with substituents selected from the  
35 group consisting of alkoxy,  
arylalkyl,

arylalkyl[S(O)<sub>q</sub>]alkyl,

aryl[S(O)<sub>q</sub>],

aryl[S(O)<sub>q</sub>]alkyl wherein the aryl[S(O)<sub>q</sub>]alkyl is

unsubstituted or substituted with 1, 2, 3, 4, or 5

substituents independently selected from

alkoxy and

loweralkyl,

arylalkoxyalkyl wherein the arylalkoxyalkyl is

unsubstituted or substituted with substituents

selected from the group consisting of

alkoxy, and

halogen,

aryloxy,

aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or

substituted with substituents selected from the

group consisting of halogen,

carboxyl,

-C(O)NR<sub>C</sub>R<sub>D</sub> wherein R<sub>C</sub> and R<sub>D</sub> are independently

selected from the group consisting of

hydrogen,

loweralkyl, and

alkoxycarbonyl or

R<sub>C</sub> and R<sub>D</sub> together with the nitrogen to which

they are attached form a ring selected

from the group consisting of

morpholine,

piperidine,

pyrrolidine

thiomorpholine,

thiomorpholine sulfone, and

thiomorpholine sulfoxide,

wherein the ring formed by R<sub>C</sub> and R<sub>D</sub>

together is unsubstituted or

substituted with 1 or 2

substituents independently

selected from the group consisting

of alkoxy and alkoxyalkyl,  
cycloalkenyl wherein the cycloalkenyl is unsubstituted or  
substituted with 1 or 2 substituents selected from  
the group consisting of alkenyl,  
5 cyclolalkoxy,  
cycloalkoxycarbonyl,  
cyclolalkoxyalkyl,  
cyclolalkyl wherein the cycloalkyl is unsubstituted or  
substituted with 1, 2, 3, 4, or 5 substituents  
10 independently selected from the group consisting  
of aryl,  
loweralkyl, and  
alkanoyl,  
cycloalkylalkoxy,  
15 cycloalkylalkoxycarbonyl,  
cycloalkylalkoxyalkyl,  
cycloalkylalkyl,  
cyclolalkyl[S(O)<sub>q</sub>]alkyl,  
cycloalkylalkyl[S(O)<sub>q</sub>]alkyl,  
20 fluorenyl,  
heterocycle wherein the heterocycle is unsubstituted or  
substituted with 1, 2, 3, or 4 substituents  
independently selected from the group  
consisting of  
25 alkoxy wherein the alkoxy is unsubstituted or  
substituted with 1 or 2 substituents  
independently selected from the group  
consisting of aryl and cycloalkyl,  
alkoxyalkyl wherein the alkoxyalkyl is  
30 unsubstituted or substituted with 1 or 2  
substituents independently selected from  
the group consisting of  
aryl and  
cycloalkyl,  
35 alkoxycarbonyl wherein the alkoxycarbonyl is  
unsubstituted or substituted with 1 or 2



substituents independently selected from  
the group consisting of  
aryl and  
cycloalkyl,  
5 aryl wherein the aryl is unsubstituted or  
substituted with 1, 2, 3, 4, or 5  
substituents independently selected from  
the group consisting of  
alkanoyl,  
10 alkoxy,  
carboxaldehyde,  
haloalkyl,  
halogen,  
loweralkyl,  
15 nitro,  
-NRR', and  
thioalkoxy,  
arylalkyl,  
aryloxy,  
20 cycloalkoxyalkyl,  
cycloalkyl,  
cycloalkylalkyl,  
halogen,  
heterocycle,  
25 hydroxyl,  
loweralkyl wherein the loweralkyl is  
unsubstituted or substituted with 1, 2, or  
3 substituents independently selected  
from the group consisting of  
30 heterocycle,  
hydroxyl,  
with the proviso that no two hydroxyls  
are attached to the same carbon,  
and  
35 -NR<sup>3</sup>R<sup>3'</sup> wherein R<sup>3</sup> and R<sup>3'</sup> are  
independently selected from the

group consisting of  
hydrogen ·  
aryl,  
loweralkyl,  
5 aryl,  
arylalkyl,  
heterocycle,  
(heterocyclic)alkyl,  
cycloalkyl, and  
10 cycloalkylalkyl, and  
sulfhydryl,  
(heterocyclic)alkoxy,  
(heterocyclic)alkyl,  
(heterocyclic)alkyl[S(O)<sub>q</sub>]alkyl,  
15 (heterocyclic)oxy,  
(heterocyclic)alkoxyalkyl,  
(heterocyclic)oxyalkyl,  
heterocycle[S(O)<sub>q</sub>]alkyl,  
hydroxyl,  
20 hydroxyalkyl,  
imino,  
N-protected amino,  
=N-O-aryl, and  
=N-OH,  
25 =N-O-heterocycle wherein the heterocycle is  
unsubstituted or substituted with 1, 2, 3, or 4  
substituents independently selected from the  
group consisting of  
loweralkyl,  
30 hydroxy,  
hydroxyalkyl,  
halogen,  
cyano,  
nitro,  
35 oxo (=O),  
-NRR'

N-protected amino,  
 alkoxy,  
 thioalkoxy,  
 haloalkyl,  
 5 carboxy, and  
 aryl,  
 =N-O-loweralkyl,  
 -NRR<sup>3</sup>R<sup>3'</sup>,  
 -NHNRCR<sub>D</sub>,  
 10 -OG wherein G is a hydroxyl protecting group,  
 -O-NH-R,  

$$-O-N \begin{array}{l} \nearrow J' \\ \searrow J \end{array}$$
 wherein J and J' are independently selected  
 from the group consisting of  
 loweralkyl and  
 15 arylalkyl,  
 oxo,  
 oxyamino(alkyl)carbonylalkyl,  
 oxyamino(arylalkyl)carbonylalkyl,  
 oxyaminocarbonylalkyl,  
 20 -SO<sub>2</sub>-A wherein A is selected from the group  
 consisting of  
 loweralkyl,  
 aryl, and  
 heterocycle  
 25 wherein the loweralkyl, aryl, and heterocycle are  
 unsubstituted or substituted with 1, 2, 3,  
 4, or 5 substituents independently  
 selected from the group consisting of  
 alkoxy,  
 30 halogen,  
 haloalkyl,  
 loweralkyl, and  
 nitro,  
 sulfhydryl,  
 35 thioxo, and

thioalkoxy,

L<sub>5</sub> is absent or selected from the group consisting of

(a) C<sub>1</sub>-to-C<sub>10</sub>-alkylene and

(b) C<sub>2</sub>-to-C<sub>16</sub>-alkenylene

5 wherein (a) and (b) are unsubstituted or substituted as defined previously, and

R<sub>5</sub> is selected from the group consisting of

hydrogen,

alkanoyl wherein the alkanoyl is unsubstituted or

10 substituted with substituents selected from the group consisting of aryl,

alkoxy,

alkoxyalkyl,

alkoxycarbonyl wherein the alkoxycarbonyl is

15 unsubstituted or substituted with 1, 2 or 3 substituents independently selected from the group consisting of aryl and halogen,

20 alkylaminocarbonylalkyl wherein the

alkylaminocarbonylalkyl is unsubstituted or

substituted with 1 or 2 substituents

independently selected from the group consisting of aryl,

25 (anthracenyl)alkyl,

aryl,

arylalkoxy,

arylalkyl wherein the arylalkyl is unsubstituted or

30 substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

alkoxy,

aryl,

carboxyl,

35 cyano,

halogen,

haloalkoxy,  
haloalkyl,  
nitro,  
oxo, and  
5 -L<sub>11</sub>-C(R<sub>14</sub>)(R<sub>v</sub>)-C(O)OR<sub>15</sub>,  
(aryl)oyl wherein the (aryl)oyl is unsubstituted or  
substituted with substituents selected from the  
group consisting of halogen,  
aryloxycarbonyl,  
10 carboxaldehyde,  
-C(O)NRR',  
cycloalkoxycarbonyl,  
cycloalkylaminocarbonyl,  
cycloalkylaminothiocarbonyl,  
15 cyanoalkyl,  
cyclolalkyl,  
cycloalkylalkyl wherein the cycloalkylalkyl is  
unsubstituted or substituted with 1 or 2 hydroxyl  
substituents,  
20 with the proviso that no two hydroxyls are attached to the  
same carbon,  
(cyclolalkyl)oyl,  
(9,10-dihydroanthracenyl)alkyl wherein the  
(9,10-dihydroanthracenyl)alkyl is unsubstituted  
25 or substituted with 1 or 2 oxo substituents,  
haloalkyl,  
heterocycle,  
(heterocyclic)alkyl wherein the (heterocyclic)alkyl is  
unsubstituted or substituted with 1, 2, 3, 4, or 5  
30 substituents selected from the group consisting of  
loweralkyl,  
(heterocyclic)oyl,  
loweralkyl, wherein the loweralkyl is unsubstituted  
or substituted with substituents selected from the  
35 group consisting of -NRR',  
-SO<sub>2</sub>-A, and

thioalkoxyalkyl;

(2)  $-L_4-O-L_5-$ ,

5 (3)  $-L_4-S(O)_m-L_5-$  wherein  $L_4$  and  $L_5$  are defined previously and  $m$  is 0, 1, or 2,

(4)  $-L_4-L_6-C(W)-N(R_6)-L_5-$  wherein  $L_4$ ,  $W$ , and  $L_5$  are defined previously,

$R_6$  is selected from the group consisting of

- 10 (a) hydrogen,  
 (b) loweralkyl,  
 (c) aryl,  
 (d) arylalkyl,  
 (e) heterocycle,  
 15 (f) (heterocyclic)alkyl,  
 (g) cyclolakyl, and  
 (h) cycloalkylalkyl, and

$L_6$  is absent or is selected from the group consisting of

- 20 (a)  $-O-$ ,  
 (b)  $-S-$ , and  
 (c)  $-N(R_6)-$  wherein  $R_6$  is selected from the group  
 consisting of  
 hydrogen,  
 loweralkyl,  
 25 aryl,  
 arylalkyl,  
 heterocycle,  
 (heterocyclic)alkyl,  
 cyclolakyl, and  
 30 cycloalkylalkyl,

(5)  $-L_4-L_6-S(O)_m-N(R_5)-L_5-$ ,

(6)  $-L_4-L_6-N(R_5)-S(O)_m-L_5-$ ,

35

(7)  $-L_4-N(R_5)-C(W)-L_7-L_5-$  wherein  $L_4$ ,  $R_5$ ,  $W$ , and  $L_5$  are

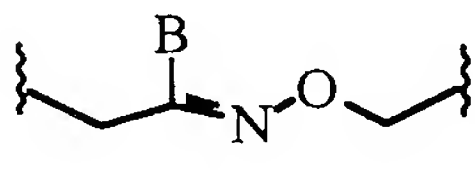
defined previously and  $L_7$  is absent or is selected from the group consisting of -O- and -S-,

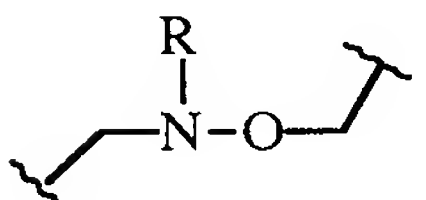
- (8)  $C_1$ - $C_{10}$ -alkylene wherein the alkylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
  - (b) arylalkyl,
  - (c) heterocycle,
  - (d) (heterocyclic)alkyl,
  - (e) cyclolalkyl,
  - (f) cycloalkylalkyl,
  - (g) alkylthioalkyl, and
  - (h) hydroxy,
- (9)  $C_2$ -to- $C_{10}$ -alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
  - (b) arylalkyl,
  - (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
  - (d) heterocycle,
  - (e) (heterocycle)alkyl,
  - (f) hydroxyalkyl,
  - (g) cyclolalkyl,
  - (h) cycloalkylalkyl,
  - (i) alkylthioalkyl, and
  - (j) hydroxy,
- (10)  $C_2$ -to- $C_{10}$ -alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,

- (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolakyl,
- (f) cycloalkylalkyl,
- (g) alkylthioalkyl, and
- (h) hydroxy,

(11) -L<sub>4</sub>-heterocycle-L<sub>5</sub>-,

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of loweralkyl and arylalkyl, and

(14)  ;

**Z** is selected from the group consisting of

- (1) a covalent bond,
- (2) -O-,
- (3) -S(O)<sub>q</sub>-, and
- (4) -NR<sub>z</sub>- wherein R<sub>z</sub> is selected from the group consisting of
  - (a) hydrogen
  - (b) loweralkyl,
  - (c) aryl,
  - (d) arylalkyl,
  - (e) heterocycle,
  - (f) (heterocyclic)alkyl,
  - (g) cyclolakyl, and
  - (h) cycloalkylalkyl;

**R<sub>3</sub>** is selected from the group consisting of

- (1) hydrogen,



- (2) aryl,
- (3) fluorenyl,
- (4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5

substituents independently selected from the group consisting of

- (a) alkanoyl,
- (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
  - halogen,
  - aryl, and
  - cycloalkyl,
- (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents independently selected from the group consisting of
  - aryl and
  - cycloalkyl,
- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
  - aryl, and
  - cycloalkyl,
- (e) alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
  - alkanoyl,
  - alkoxy wherein the alkoxy is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of cycloalkyl,
  - carboxaldehyde,
  - haloalkyl,
  - halogen,
  - loweralkyl,
  - nitro,

- NRR', and  
thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or  
5 substituted with 1, 2, 3, 4, or 5 substituents  
independently selected from the group consisting of,  
halogen,  
nitro, and  
-NRR',
- (j) (aryl)oyl,
- (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR" wherein R is defined previously and R" is  
15 selected from the group consisting of  
hydrogen,  
loweralkyl, and  
carboxyalkyl,
- (o) cyano,
- (p) cyanoalkyl,
- (q) cycloalkyl,
- (r) cycloalkylalkyl,
- (s) cycloalkoxyalkyl,
- (t) halogen,
- (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted  
25 with 1, 2, 3, 4, or 5 hydroxyl substituents,  
with the proviso that no two hydroxyls are attached to the same  
carbon,
- (v) heterocycle,
- (w) hydroxyl,
- (x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or  
substituted with substituents selected from the group  
consisting of aryl,
- (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted  
35 with substituents selected from the group consisting of  
heterocycle,

hydroxyl,

with the proviso that no two hydroxyls are attached to the  
same carbon,

$-\text{NR}^{\text{R}^3}\text{R}^{\text{R}^3'}$ , and

$-\text{P}(\text{O})(\text{OR})(\text{OR}')$ ,

(z) nitro,

(aa)  $-\text{NRR}'$ ,

(bb) oxo,

(cc)  $-\text{SO}_2\text{NR}_\text{A}'\text{R}_\text{B}'$  wherein  $\text{R}_\text{A}'$  and  $\text{R}_\text{B}'$  are independently selected

from the group consisting of

hydrogen,

(aryl)oyl,

loweralkyl, and

heterocycle wherein the heterocycle is unsubstituted or

substituted with 1, 2, or 3 substituents

independently selected from the group consisting

of loweralkyl,

(dd) sulfhydryl, and

(ee) thioalkoxy,

(5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with  
1, 2, 3, 4 or 5 substituents selected from the group consisting of

(a) alkoxy,

(b) aryl,

(c) arylalkoxy

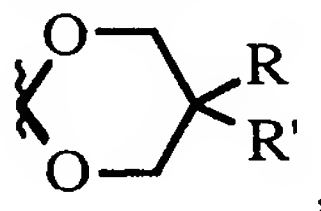
(d) aryloxy wherein the aryloxy is unsubstituted or  
substituted with 1, 2, 3, 4, or 5 substituents  
selected from the group consisting of halogen,

(e) loweralkyl,

(f) halogen,

(g)  $\text{NR}^{\text{R}^3}\text{R}^{\text{R}^3'}$ ,

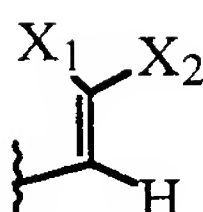
(h) oxo, and

(i) ,

(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted

with 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (a) loweralkyl,
- (b) alkoxy,
- (c) halogen,
- (d) aryl,
- (e) aryloxy,
- (f) alkanoyl, and
- (g)  $\text{NR}^3\text{R}^{3'}$ ,

- (7)  wherein  $\text{X}_1$  and  $\text{X}_2$  together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

- (8)  $-\text{P}(\text{W})\text{R}^3\text{R}^{3'}$ ; and

$\text{R}_4$  is selected from the group consisting of

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl
- (4) halogen,
- (5) aryl,
- (6) arylalkyl,
- (7) heterocycle,
- (8) (heterocyclic)alkyl
- (9) alkoxy, and
- (10)  $-\text{NRR}'$ ; or

$\text{L}_1$ ,  $\text{Z}$ , and  $\text{R}_3$  together are selected from the group consisting of

- (1) aminoalkyl,
- (1) haloalkyl,
- (2) halogen,
- (3) carboxaldehyde, and
- (4) (carboxaldehyde)alkyl, and

(5) hydroxyalkyl,  
with the proviso that when  $L_1$ ,  $Z$ , and  $R_3$  together are (1)-(5),  $R_1$  is other than hydrogen.

2. A compound according to claim 1 wherein  $L_1$  is selected from the group consisting of

(1)  $-L_4-L_6-S(O)_m-N(R_5)-L_5-$ ,

5 (2)  $-L_4-L_6-N(R_5)-S(O)_m-L_5-$ ,

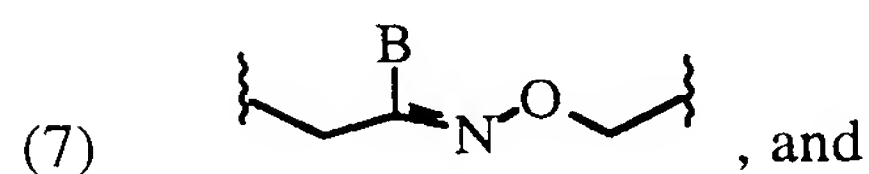
(3)  $C_1-C_{10}$ -alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

10 (4)  $C_2$ -to- $C_{16}$ -alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

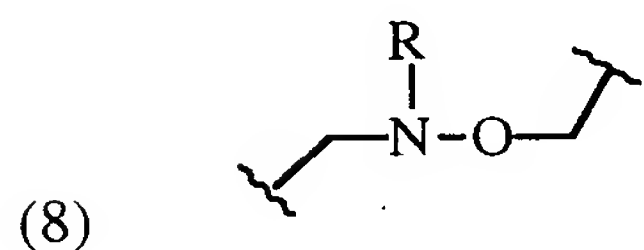
(5)  $C_2$ -to- $C_{10}$ -alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

15

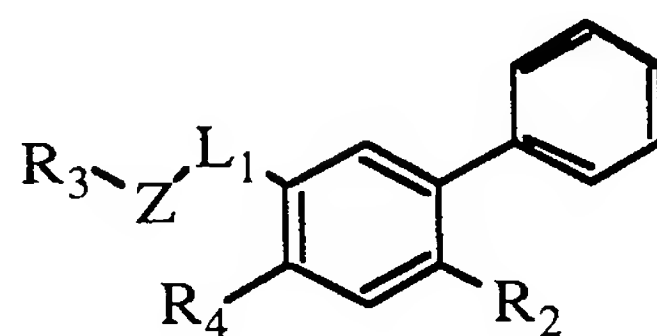
(6) a covalent bond,



20



3. A compound according to claim 1 of formula



wherein

$R_3$  is selected from the group consisting of

5 (1) hydrogen,

(2) aryl,

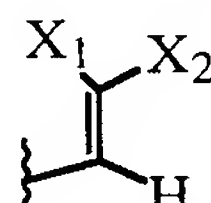
(3) fluorenyl,

(4) heterocycle

wherein (2)-(4) are unsubstituted or substituted as defined previously,

10 (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and

(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously,

(7)  , and

15

(8)  $-P(W)R^3R^{3'}$ ; and

$L_1$  is selected from the group consisting of

(1)  $-L_4-L_6-S(O)_m-N(R_5)-L_5-$ ,

20

(2)  $-L_4-L_6-N(R_5)-S(O)_m-L_5-$ ,

(3)  $C_1-C_{10}$ -alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,


25

(4)  $C_2$ -to- $C_{16}$ -alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

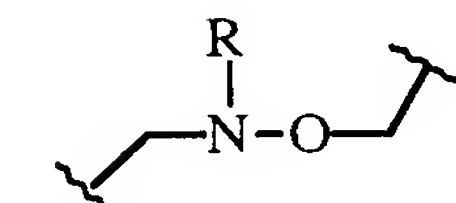
(5)  $C_2$ -to- $C_{10}$ -alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

30

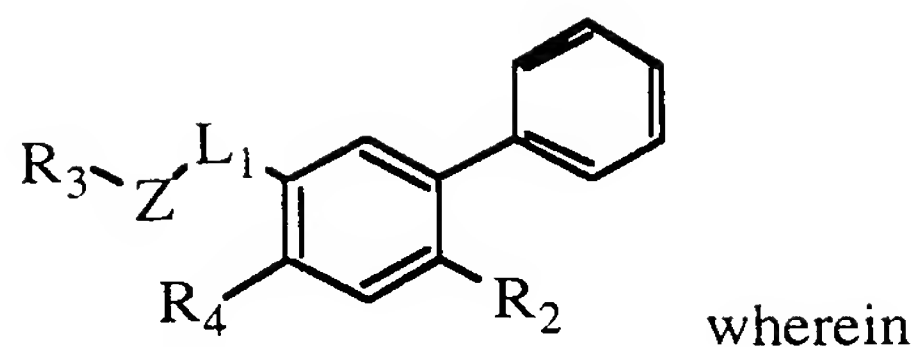
(6) a covalent bond,

(7)  , and

35

(8)  .

4. A compound according to claim 1 of formula

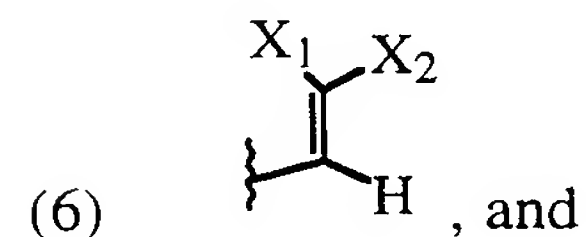


**R<sub>3</sub>** is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,

wherein (2) and (3) are unsubstituted or substituted as defined previously,

- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously,



- (7) -P(W)R<sup>3</sup>R<sup>3'</sup>; and

**L<sub>1</sub>** is selected from the group consisting of

- (1) -L<sub>4</sub>-L<sub>6</sub>-S(O)<sub>m</sub>-N(R<sub>5</sub>)-L<sub>5</sub>-,

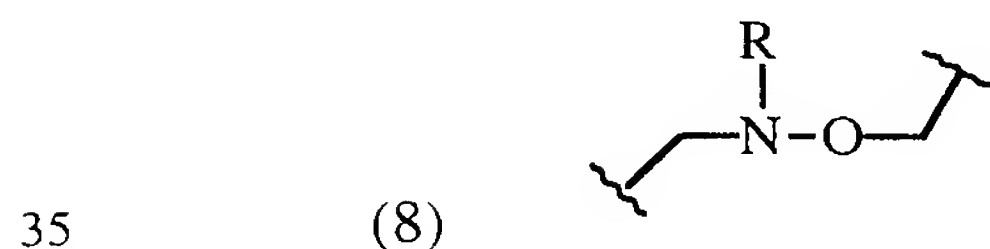
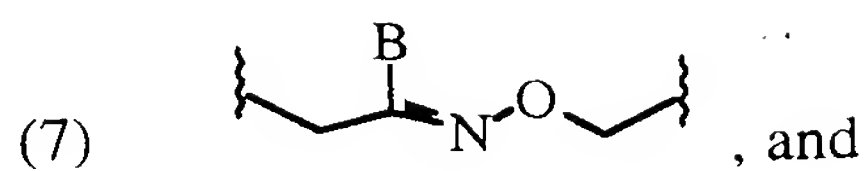
- (2) -L<sub>4</sub>-L<sub>6</sub>-N(R<sub>5</sub>)-S(O)<sub>m</sub>-L<sub>5</sub>-,

- (3) C<sub>1</sub>-C<sub>10</sub>-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

- (4) C<sub>2</sub>-to-C<sub>16</sub>-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

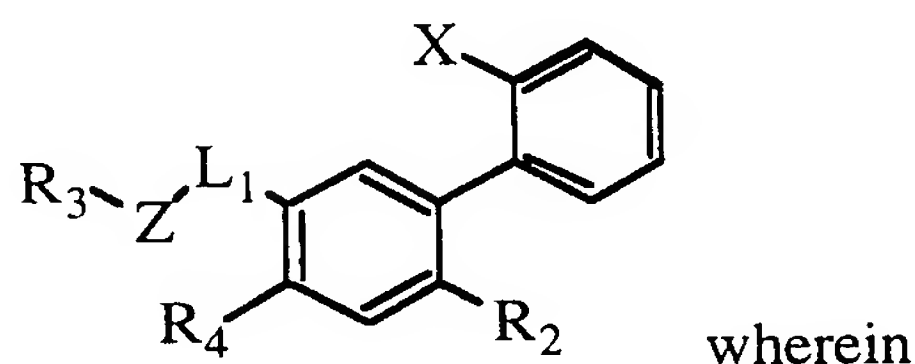
- (5) C<sub>2</sub>-to-C<sub>10</sub>-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

- (6) a covalent bond,



5. A compound according to claim 3 selected from the group consisting of  
 [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine,  
 hydrochloride ,  
 [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine,  
 5 (4-piperazinylmethyl-2-phenylbenzoyl)methionine, and  
 [4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine.

6. A compound according to claim 1 of formula



**R<sub>3</sub>** is selected from the group consisting of

- 5 (1) hydrogen,  
 (2) aryl,  
 (3) fluorenyl,  
 (4) heterocycle

wherein (2)-(4) are unsubstituted or substituted as defined previously,

- 10 (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as  
 defined previously, and  
 (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as  
 defined previously;

15 **L<sub>1</sub>** is selected from the group consisting of

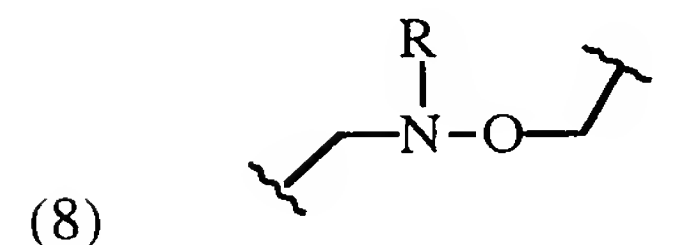
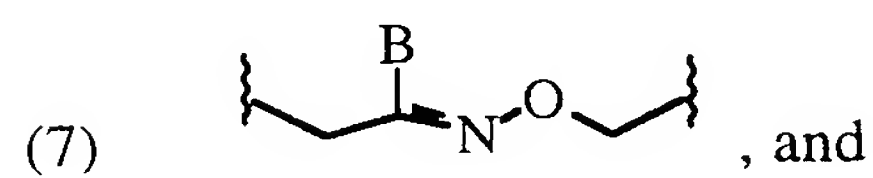
- (1) -L<sub>4</sub>-L<sub>6</sub>-S(O)<sub>m</sub>-N(R<sub>5</sub>)-L<sub>5</sub>-,  
 (2) -L<sub>4</sub>-L<sub>6</sub>-N(R<sub>5</sub>)-S(O)<sub>m</sub>-L<sub>5</sub>-,



- 20 (3) C<sub>1</sub>-C<sub>10</sub>-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,
- (4) C<sub>2</sub>-to-C<sub>16</sub>-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,
- 25 (5) C<sub>2</sub>-to-C<sub>10</sub>-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

(6) a covalent bond,

30



35 **Z** is a covalent bond; and

**X** is selected from the group consisting of

alkoxy,

aryl,

40 carboxy,

cyano,

halogen,

haloalkyl,

hydroxy,

45 hydroxyalkyl,

loweralkyl,

nitro,

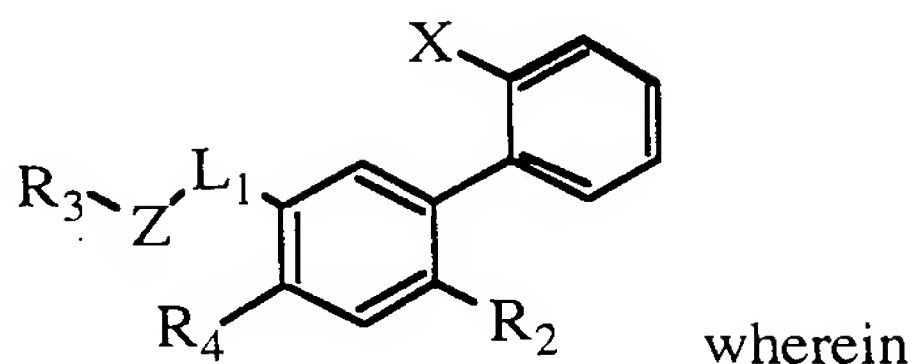
N-protected amino,

-NRR,

50 oxo (=O), and

thioalkoxy.

7. A compound according to claim 1 of formula



**R<sub>3</sub>** is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,

wherein (2) and (3) are unsubstituted or substituted as defined previously,

- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and

- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

**L<sub>1</sub>** is selected from the group consisting of

- (1) -L<sub>4</sub>-L<sub>6</sub>-S(O)<sub>m</sub>-N(R<sub>5</sub>)-L<sub>5</sub><sup>-</sup>,

- (2) -L<sub>4</sub>-L<sub>6</sub>-N(R<sub>5</sub>)-S(O)<sub>m</sub>-L<sub>5</sub><sup>-</sup>,

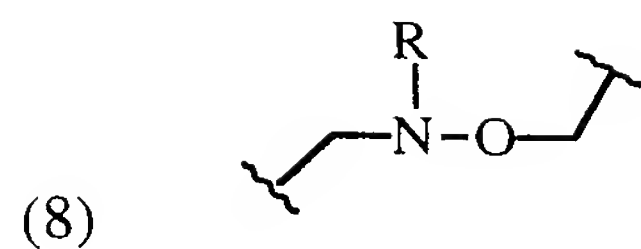
- (3) C<sub>1</sub>-C<sub>10</sub>-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

- (4) C<sub>2</sub>-to-C<sub>16</sub>-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

- (5) C<sub>2</sub>-to-C<sub>10</sub>-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

- (6) a covalent bond,

- (7) , and



**Z** is a covalent bond; and

**X** is selected from the group consisting of

alkoxy,

aryl,

carboxy,

cyano,

halogen,

haloalkyl,

hydroxy,

hydroxyalkyl,

loweralkyl,

nitro,

N-protected amino,

-NRR,

oxo (=O), and

thioalkoxy.

8. A compound according to claim 5 wherein **X** is selected from the group consisting of loweralkyl.
9. A compound according to claim 7 selected from the group consisting of
  - [4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
  - N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
  - lithium salt,
  - N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine,
  - lithium salt,
  - N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
  - N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
  - lithium salt,

- N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- 15 N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 20 N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 25 N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- N-[4-(2-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 30 N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 35 N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 40 N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 45 N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(4-cyclohexylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

- N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt,
- 50 N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,
- 55 N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
60 lithium salt,  
N-[4-(N-benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine,  
lithium salt,
- 65 N-[4-(1-benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine,  
lithium salt,  
N-[4-N-(2-piperidin-1-ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,  
lithium salt,  
N-[4-N-(2-morpholin-1-ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,  
70 lithium salt,  
N-[4-(2-(3,4-dimethoxyphenyl)ethylaminosulfonyl)-2-phenylbenzoyl]-  
methionine, lithium salt,  
N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]-  
methionine, lithium salt,
- 75 N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,  
N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 80 N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,

- 85 N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,  
90 lithium salt,  
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)-  
benzoyl]methionine, lithium salt,  
95 N-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)-  
benzoyl]methionine, lithium salt,  
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethyl)-2-(2-methylphenyl)benzoyl]-  
100 methionine, lithium salt,  
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-  
benzoyl]methionine ,  
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-  
benzoyl]methionine,  
105 N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-  
benzoyl]methionine,  
N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-  
110 methionine,  
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-  
benzoyl]methionine,  
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
115 N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-  
benzoyl]methionine,  
N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)-

- 120 benzoyl]methionine,  
N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
N-[4-N-(1,3-diphenylpropan-2-yl)iminooxymethyl-2-(2-methylphenyl)  
benzoyl]-methionine, lithium salt,
- 125 N-[4-(N-hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
N-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine ,  
N-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine ,
- 130 N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)-  
benzoyl]methionine ,  
N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine ,
- 135 N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine ,  
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-  
benzoyl]methionine ,  
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-  
benzoyl]methionine, lithium salt,
- 140 N-[4-(4-benzylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,
- 145 N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,  
N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,
- 150 N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,  
N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,
- 155 N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-

methionine,

N-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine,

N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-  
2-(2-methylphenyl)benzoyl]methionine,

N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-  
benzoyl]methionine,

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-  
-2-(2-methylphenyl)benzoyl]methionine,

N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-  
methylphenyl)benzoyl]methionine,

N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-  
benzoyl]methionine,

N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-  
benzoyl]methionine,

N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-



- methylphenyl)benzoyl]methionine,  
 N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)-  
 benzoyl]methionine,  
 195 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-  
 methylphenyl)benzoyl]methionine, lithium salt,  
 N-[4-(N-cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)-  
 benzoyl]methionine, lithium salt,  
 N-{4-[E-2-hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-  
 200 methylphenyl)benzoyl}methionine, lithium salt,  
 N-{4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)-  
 prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine, lithium salt,  
 N-[4-N--benzyloxy-N-butylaminomethyl-2-(2-methylphenyl)benzoyl]-  
 methionine, lithium salt,  
 205 N-[4-N--butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-  
 methylphenyl)benzoyl]methionine, lithium salt,  
 N-[4-N--butyl-N-(cyclohexylmethyloxy)aminomethyl-2-(2-methylphenyl)-  
 benzoyl]methionine, lithium salt,  
 N-[4-N--butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)-  
 210 benzoyl]methionine, lithium salt,  
 N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-  
 methionine,  
 N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-  
 methionine,  
 215 N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-  
 methylphenyl)benzoyl]methionine,  
 N-[4-((cyclohexylmethyl)methyl (oxophosphinyl)methyl)-2-(2-methyl-  
 phenyl)benzoyl]methionine,  
 N-[4-((cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-  
 220 methylphenyl)benzoyl]methionine,  
 N-[4-(di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)-  
 benzoyl]methionine,  
 N-[4-(di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)-  
 benzoyl]methionine,  
 225 N-[4-(di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)-  
 benzoyl]methionine,  
 N-[4-(dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-

- methionine,  
 N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine, lithium  
 230 salt.,  
 N-[4-(2-(2-cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)-  
 benzoyl]methionine, lithium salt,  
 N-[4-(2-(2-cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)-  
 benzoyl]methionine, lithium salt,  
 235 N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)-  
 benzoyl]methionine, lithium salt, and  
 N-[4-(4-cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)-  
 benzoyl]methionine, lithium salt.
10. A compound selected from the group consisting of  
 [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine,  
 hydrochloride,  
 [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine,  
 (4-piperazinylmethyl-2-phenylbenzoyl)methionine,  
 [4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine,  
 [4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-  
 methionine,  
 N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,  
 lithium salt,  
 N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine,  
 lithium salt,  
 N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-  
 methylsulfinylbutanoic acid, lithium salt,  
 N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,  
 lithium salt,  
 N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-  
 methylsulfinylbutanoic acid, lithium salt,  
 N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine,  
 lithium salt,  
 N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine,  
 lithium salt,  
 N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,

lithium salt,  
N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,  
N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine , lithium salt,  
N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,  
N-[4-(2-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(4-cyclohexylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt,  
N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(N-benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine,  
lithium salt,  
N-[4-(1-benzylylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine,  
lithium salt,  
N-[4-N-(2-piperidin-1ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,  
lithium salt,  
N-[4-N-(2-morpholin-1ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,  
lithium salt,  
N-[4-(2-(3,4-dimethoxyphenyl)ethylaminosulfonyl)-2-phenylbenzoyl]-  
methionine, lithium salt,  
N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]-  
methionine, lithium salt,  
N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,  
N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,  
N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-  
methionine, lithium salt,  
N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,  
lithium salt,

N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,  
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,  
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,  
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,  
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-N-(1,3-diphenylpropan-2-yl)iminooxymethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,  
N-[4-(N-hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]-methionine,

N-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,  
N-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,  
N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,  
N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,  
N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,  
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,  
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(4-benzylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,  
N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(2-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,



N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-benzyloxymethyl-4-methoxypyrrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-benzyloxymethyl-4-methoxypyrrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(N-cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-{4-[E-2-hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine, lithium salt,  
N-{4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)-prop-2-enyl]-2-(2-methylphenyl)benzoyl}methionine, lithium salt,  
N-[4-N-benzyloxy-N-butylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,  
N-[4-N-butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-N-butyl-N-(cyclohexylmethoxy)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-N-butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-((cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,  
N-[4-(dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-methionine,  
N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine, lithium salt.,  
N-[4-(2-(2-cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,  
N-[4-(2-(2-cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,



N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt, and  
N-[4-(4-cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt.

11. A method of inhibiting protein isoprenyl transferases in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
12. A composition for inhibiting protein isoprenyl transferases comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.
13. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
14. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
15. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 16. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 17. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
18. A composition for treating or preventing restenosis in a mammal comprising a

compound of claim 1 in combination with a pharmaceutically acceptable carrier.

15. A method of inhibiting protein isoprenyl transferases in a mammal in need of , such treatment comprising administering to the mammal a therapeutically , effective amount of a compound of claim 1.
16. A composition for inhibiting protein isoprenyl transferases comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.
17. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
18. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
19. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 20. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 21. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
22. A composition for treating or preventing restenosis in a mammal comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/09297

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN, 1997:247953, BOYLE, F.t. et al., 'Preparation of 2-aminomethyl-4-mercaptopyrrolidines and analogs as farnesyl transferase inhibitors', 20 February 1997, PCT Int. Appl. 189 pp., see entire abstract.	1-22
X	Database HCAPLUS on STN, 1996:567259, SEBTI et al., 'Peptidomimetic inhibitors of prenyl transferases, preparation and activity of the peptidomimetics, and use for treating tumors', 18 July 1996, PCT Int. Appl. 186 pp., see entire abstract.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 SEPTEMBER 1998

Date of mailing of the international search report

19 OCT 1998

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/09297

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/38, 31/39, 31/40, 31/415, 31/42, 31/425, 31/44, 31/445, 31/495, 31/505, 31/095, 31/18; C07D 207/09, 233/54, 239/24, 241/04, 263/02, 277/28, 307/00, 333/00, 209/10; C07C 303/00, 307/00, 309/00, 313/00

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400; 546/225, 300, 312, 336; 548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49

## B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400; 546/225, 300, 312, 336; 548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49